January 2010

BioSupply Trends

Special Focus: PLASMA

Quarterly

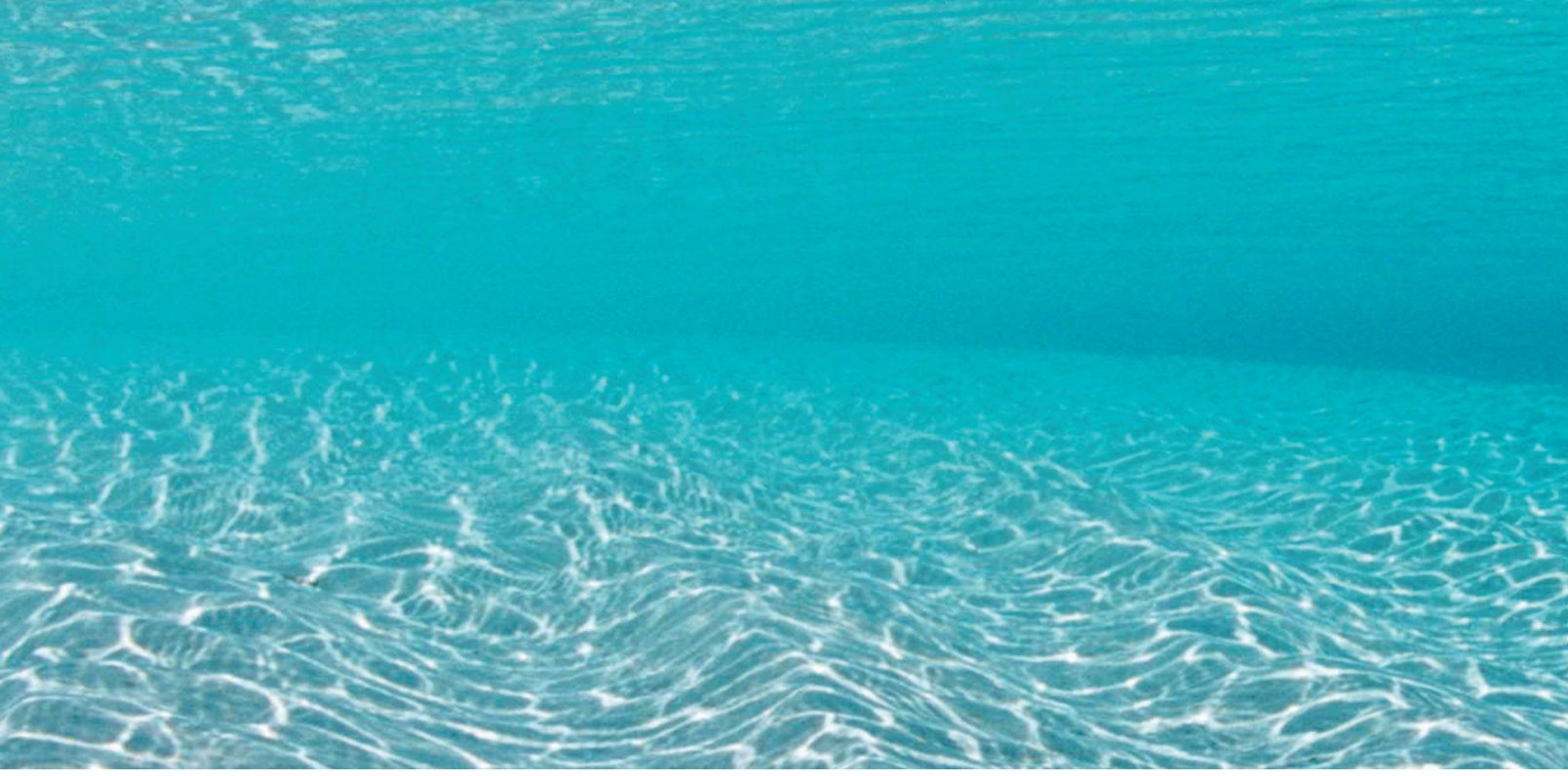
Plasma Therapies

IG in the Driver's Seat

IVIG Research: The New Frontier

Coagulation Products On the Horizon

Myths and Facts: Meningitis — Page 38



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use octagam®, Immune Globulin Intravenous (Human), safely and effectively.

OCTAGAM®
Immune Globulin Intravenous (Human) 5% Liquid Preparation

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Warnings and Precautions - Hyperproteinemia 8/2008

WARNING: ACUTE RENAL DYSFUNCTION and RENAL 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. octagam® 5% liquid does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

INDICATIONS AND USAGE

- octagam® is an immune globulin intravenous (human), 5% liquid, indicated for treatment of primary humoral immunodeficiency (PI).

DOSAGE FORMS AND STRENGTHS

octagam® 5% liquid is supplied in 1.0 g, 2.5 g, 5 g , 10 g or 25 g single-use bottles

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity
- Patients with acute hypersensitivity reaction to corn

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 and serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Falsely elevated blood glucose readings may occur during and after the infusion of octagam® 5% liquid with some glucometer and test strip systems.
- 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 octagam® 5% liquid 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

Most common adverse reactions with an incidence of > 5% during a clinical trial were headache and nausea. To report SUSPECTED ADVERSE REACTIONS, contact Octapharma at 1-866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- The passive transfer of antibodies may confound the results of serological testing.
- The passive transfer of antibodies may interfere with the response to live viral vaccines.

USE IN SPECIFIC POPULATIONS

- Pregnancy: no human or animal data. Use only if clearly needed.
- In patients over age 65 or in any person at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse octagam® 5% liquid at the minimum infusion rate practicable.

HOW SUPPLIED

	1g	2.5g	5g	10g	25g
Size	20ml	50ml	100ml	200ml	500ml
NDC#	67467-843-01	67467-843-02	67467-843-03	67467-843-04	67467-843-05
NDC#	68209-843-01	68209-843-02	68209-843-03	68209-843-04	

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www.octapharma.com/usa

A clear solution

IMPORTANT SAFETY INFORMATION

octagam® is contraindicated in individuals with intolerance to immunoglobulins, especially in immunoglobulin A (IgA) deficiency, when the patient has IgE mediated antibodies to IgA. Immune Globulin intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Other possible side effects with octagam® include: aseptic meningitis, hemolysis, transfusion-related acute lung disease (TRALI) and thrombotic events.

Immune Globulin Intravenous (Human) products have been reported to be associated with various minor reactions, such as headache, chills, backache, chest pain, fever, allergic reactions, arthralgia, dizziness, changes in blood pressure, cutaneous reactions and/or nausea and vomiting. Cases of reversible aseptic meningitis and migraine and isolated cases of reversible hemolytic anemia and reversible increases in liver function tests have been observed with octagam®. Immediate anaphylactic and hypersensitivity reactions are a remote possibility.

As with all medicines made from human plasma, the risk of spreading infectious agents, including viruses, cannot be completely eliminated.

Some types of blood glucose testing systems falsely interpret the maltose contained in octagam® as glucose. This has resulted in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia.

See brief summary of PI on facing page.

Ochs HD, Pinciaro PJ and the octagam® Study Group. octagam® 5%, an Intravenous IgG Product, is Efficacious and Well Tolerated in Subjects with Primary Immunodeficiency Diseases. *J. Clin Immunol* 2004,24;3:309-314

octagam®

Immune globulin intravenous (human)
5% liquid preparation

If you've been looking for an IGIV solution, take a look at octagam®.

octagam® is safe and effective for treatment of PID. *(See important safety information)*

octagam® is carefully produced to retain as many of the characteristics of natural plasma as possible.

With over 40 million grams of octagam® infused world-wide, Octapharma is committed to helping PI patients live more active and healthier lives.

Ask your health care provider today about octagam® and find out if it could be the right solution for you.

For clinical or technical questions, please call our Medical Affairs team at 888-429-4535.

To order call FFF at 1-800-843-7477.

octapharma

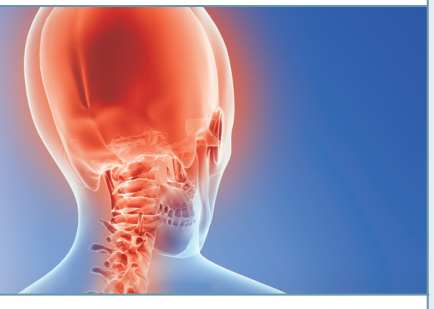
For the safe and optimal use of human proteins

BioSupply Trends Quarterly

January 2010

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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Patients First

JUST A FEW short weeks ago, a young man who is now 18 and living with primary immune deficiency disease (PIDD) graced our company with a visit to talk with our teams. While I have been blessed to meet many such patients over the course of my more than 21 years of experience in this industry, each encounter is a reminder of how critical what we do is to so many, and how far we have come despite many obstacles. As this young man and his parents described their experiences throughout the years — from the difficulty in arriving at an accurate diagnosis, to individually and collectively as a family dealing with obtaining and administering immune globulin (IG) — it was apparent that our obstacles are minor compared to those that the chronically ill are faced with each and every day.

This young man has made it part of his life's mission to help others better understand how essential their help is to him and others like him. He frequents plasma collection centers to thank donors and to show them the end result of their actions — the impact their donations have made on his life and the lives of many others — rewarding those donors with insight that is far more valuable than the check they will receive. During his visit to our company, he demonstrated how he is now able to self-infuse subcutaneous IG (SCIG), illustrating the impact this treatment has had on his lifestyle, and reminding us how many donors are needed for just one patient's weekly treatments.

Keeping a patient focus and understanding how pharmaceutical advances have improved the quality of life for patients is illustrated in this issue's article, Better by Design: New Coagulation Products on the Horizon. In the early 1960s, the outlook was grim for young males with hemophilia; yet just five years later, those same boys' odds improved dramatically, and today, the availability of safe therapies and the ease of their administration have had remarkable impact on these patients' quality of life. As this article highlights, the best may be yet to come, with astounding scientific breakthroughs showing great promise in clinical trials.

Also in this issue, we look at the intricate process of producing plasma protein therapies — from collection to fractionation to manufacturing — in our article, Plasma Therapies: IG in the Driver's Seat. Because production of these therapies differs so significantly from traditional pharmaceutical manufacturing, and is tied to the fragile economics dependent on demand for all of the plasma derivatives, its complexity is often misunderstood, adding to reimbursement concerns.

The topic of reimbursement is always front burner as issues continue to heat up with healthcare reform. Unfortunately, those with chronic and rare diseases continue to be left out of the discussion on such important topics as unaffordable copays/coinsurance, lifetime caps, step therapy and brand switching. Our new column, Reimbursement FAQs, tackles some reimbursement questions. While this issue's column focuses on IG, future columns will answer some of the most commonly misunderstood questions about reimbursement for all types of therapies. In addition, our new Reimbursement Unraveled teleforums have been created to continue the dialogue about the complex issues that healthcare providers face in being reimbursed for these critical therapeutics.

As always, we hope you find this issue of *BioSupply Trends Quarterly* informative, insightful and useful to you and your colleagues. ❖

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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Healthcare Reform Issues for Chronic and Rare Diseases

THE PASSAGE OF a healthcare reform bill to increase benefits for the uninsured and underinsured still leaves unchanged issues faced by patients who have chronic and rare diseases and rely on expensive therapies. For these patients and their healthcare providers, the following concerns remain to be addressed in later legislation:

Unaffordable Copays/Coinsurance. Patients' copays for their lifesaving therapies will increase, and many of these therapies will now fall under coinsurance that requires patients to pay 10 percent to 30 percent of the cost of the drug instead of a set amount. Because of this, patients will not be able to afford treatments.

Lifetime Caps. While these caps remain, it's important that patients look at their insurance plan choices and know when they are going to reach their lifetime cap. When offered a choice between plans, such as HMOs and PPOs, patients sometimes have the option to switch during open season from one plan to the other, which could bring their lifetime cap expenses down to zero for that year. They can then switch back the next year to the preferred plan, again possibly zeroing out the expenses counted toward the lifetime cap. However, before making any changes, patients should first check with their insurance providers to determine whether making a switch would indeed affect their lifetime cap.

Step Therapy. To keep costs down, payers will require patients to undergo step therapy, even if it is contrary to their treating physician's recommendation. To best defend against this strategy, patients must keep good notes, copies of lab work and medical journal articles that discuss the best treatments for their disease to be ready to appeal their insurance company's denials.

Comparative Effectiveness versus Cost Effectiveness. Funding continues for comparative effectiveness research, which can determine health outcomes data on the best therapies for patients. If used correctly, comparative effectiveness can be a beneficial tool for patients. However, it depends on who is conducting the studies and for what reasons. For instance, comparing the long-term effects of intravenous immune globulin (IVIG) versus steroids for certain autoimmune diseases can help ensure coverage for patients and potentially result in new IVIG indications approved by the FDA.

Brand Switching. Payers are continuing to switch the type of prescriptions patients receive without prior knowledge of their physicians. This includes switching brand products to generics, as well as to different classes of drugs. In addition, patients who rely on plasma-derived therapies, such as IVIG and biologics, have been told their product is no longer available. In many cases, physicians are not aware of the change in product until patients have an adverse reaction. While the goal of payers is to save money, this practice puts patients' health at risk.

Some of these issues need to be addressed on the federal level, while others need legislation at the state level. 2010 is the year for the plasma, biologics and vaccine communities to come together to ensure the voices of patients and providers are heard. ❖

Medicare Part D Drug Plan Premiums Rise

Monthly premiums for Medicare beneficiaries who are enrolled in Part D stand-alone prescription drug plans will rise 11 percent on average to $38.85 in 2010 if beneficiaries stay in their current plans, according to a new Kaiser Family Foundation analysis. Average monthly premiums have gone up by 50 percent for stand-alone Part D prescription drug plans since the launch of Medicare's drug benefit in 2006, when monthly premiums averaged $25.93.

As many as 1.2 million people on Medicare will see monthly premiums increase by at least $10 unless they switch to a less-expensive plan. Many of these individuals will also receive lower Social Security checks because their Part D premiums are deducted directly from their payments, and there will be no cost-of-living increase for Social Security in 2010.

In addition, for the first time since the Medicare drug benefit launched, a majority of stand-alone drug plans (61 percent) will require enrollees to meet a deductible before coverage begins, up from 45 percent last year and 42 percent in 2006.

The vast majority (80 percent) of all stand-alone Part D plans will have a gap in coverage, known as the "doughnut hole," up from 75 percent last year. When enrollees reach the gap, they will have to pay the full price of their medications. And, coverage will be limited to generic drugs for the 20 percent of stand-alone plans with some coverage in the gap. Although members of Congress proposed different options to remove the doughnut hole and decrease premiums, none of the health insurance reform proposals do either. However, options do exist to decrease the coverage gap (doughnut hole).

Changes in Medicare Part D and other healthcare plans also shift some coverages to Tier IV and V drug benefit plans. These coverages include plasma therapies, biologics and other expensive therapies that will no longer be covered under major medical or Tier I, II and III drug plans in which patients are responsible to pay a standard copay. Instead, patients now may be forced to pay coinsurance, which is 10 percent to 30 percent of the cost of the drug. ❖

Alliance Receives Nonprofit Status

The Alliance for Plasma Therapies

The Alliance for Plasma Therapies received its 501(c)(3) nonprofit status from the Internal Revenue Service in April 2009. Formed in 2007, the group's mission is to provide a unified, powerful voice of patient organizations, healthcare providers and industry leaders to educate about the diseases that rely on plasma-derived therapies and advocate for fair access to plasma therapies for patients who benefit from their lifesaving effects. Some of the current issues the alliance is working on include the increased number of patients being denied access to treatments prescribed by their physicians; lack of understanding of the diseases that rely on plasma-derived therapies; need for patient access to all sites of care; disruption of the sacred relationship between the patient and physician; understanding how plasma-derived therapies work; and safety and efficacy of plasma.

The alliance continues to assist patients in obtaining access to prescribed therapies, as well as educate members of Congress, governmental agencies, media and the public about the importance of plasma therapies and the rare diseases that rely on these lifesaving therapies. Current members include the American Autoimmune Related Diseases Association, America's Blood Centers, American Partnership of Eosinophilic Disorders, American Society of Clinical Oncology, ASD Healthcare, A-T Children's Foundation, FFF Enterprises, Foundation for Peripheral Neuropathy, IgG America, Infusion Nurses Society, International Pemphigus & Pemphigoid Foundation, Michigan Immunodeficiency Foundation, The Myositis Association, Neuropathy Action Foundation, The Neuropathy Association, NuFACTOR, Octapharma, Platelet Disorder Support Association, Stiff Person Syndrome Support Group and U.S. BioServices. ❖

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

Supplier

Hemophiliacs Eligible for College Scholarships

College students with hemophilia or a related bleeding disorder and their family members are eligible to apply for the Eric Dostie Memorial College Scholarship. The scholarship will award $1,000 each to 10 students who can best demonstrate scholastic achievement, community service and financial need. Applicants must submit an essay describing how their education will be used to serve humankind and to encourage self-improvement and enrichment.

The annual scholarship is made possible by NuFACTOR, the specialty pharmacy subsidiary of FFF Enterprises Inc., Temecula, Calif., the nation's leading distributor of critical-care plasma products, antihemophilic factors and

preventive vaccines. The scholarship was created to honor the memory of Eric Steven Dostie of Easthampton, Mass., a 5-year-old boy with hemophilia, who was tragically murdered on August 27, 1994. Eric's brief life forever touched many others with joy, humor and unending love. Eric used to tell his parents and grandparents that he might grow up to be a scientist and invent a cure for hemophilia in the form of a "chocolate pill." Although Eric's dream will never be realized, it has the chance to live on in the recipients of the award, who pursue a college degree to broaden their education and career opportunities.

To be eligible to apply, students must be citizens of the United States and enrolled full-time in an accredited two- or four-year college program. The scholarship application deadline is March 1, 2010. An application can be accessed at www.NuFACTOR.com. ❖

Research

Companies Struggle to Improve Supply Chain

More than 50 percent of executives at leading companies in the global pharmaceutical, biotechnology, medical device and consumer healthcare industries say their companies fail to respond quickly enough to pandemics and other emergencies because of lapses in their supply chain. This and other key findings are revealed in a new study by IBM that surveyed top supply chain executives to examine how well they are doing at planning, logistics, procurement and coordination throughout the life cycle of their products.

Titled "The Smarter Supply Chain of the Future: Life Sciences Edition," the global study also revealed that tracking every step of how drugs are manufactured and distributed is a key priority for more than 70 percent of companies. Yet, while the industry is far ahead of most others when it comes to supply chain planning with suppliers, the study indicates the industry falls far behind on collaborating with customers on demand planning, forecasting and replenishment — all critical steps to rapidly responding with new vaccines in the event of pandemics, and to ensure that demand does not outstrip supply.

Part of the supply chain problem is that more pharmaceutical companies are selling drugs, devices, therapies and services supplied by different partners. In addition, they are serving smaller patient segments, rather than relying on major new drug discoveries that drive revenue over many years. "The companies we spoke with said they are looking to a different kind of supply chain — one that gives the insight to react instantly to risks or threats, is much smarter and [is] able to provide them the insight and agility necessary to compete in a changing marketplace," said Dr. Philippe Cini, IBM Global Business Services, Life Sciences Supply Chain Management Partner.

Counterfeiting is one of the biggest risks facing the pharmaceutical industry today, and according to the World Health Organization, approximately 10 percent of the worldwide drug supply is counterfeit. To combat such risks, sophisticated simulations and data models can help companies calculate risk, and intelligent products and packaging devices, such as barcodes, RFID tags and other smart devices, can prevent theft.

An indepth report on securing the supply chain through e-pedigree and track-and-trace capabilities was published in the October 2009 issue of *BioSupply Trends Quarterly* on page 50. For more information about the IBM study, go to ibm.com/supplychainstudy. ❖

Supplier

Octapharma Applies to FDA for New IVIG Drug

Octapharma AG recently submitted its biological license application for Octagam 10% (human normal intravenous immunoglobulin, liquid) to the U.S. Food and Drug Administration as part of its goal to expand the company's U.S. immune globulin therapy portfolio by early 2010. The application was submitted for the treatment of idiopathic thrombocytopenic purpura (ITP), a blood-clotting disorder that can result in excessive bruising and bleeding.

"The expected introduction of Octagam 10% will provide yet another immune globulin intravenous (IVIG) product option for patients that further builds on the success already achieved with the Octagam product line both globally and in the U.S.," said Octapharma USA President Flemming Nielsen.

The company also recently submitted an investigational new drug (IND) application for a next-generation IVIG product for the treatment of ITP and chronic inflammatory demyelinating

polyneuropathy (CIDP), a neurological disorder that progressively impairs leg and arm function. In addition, Octapharma is evaluating the efficacy of immune globulin as a treatment in new and existing conditions, including ITP, CIDP, multiple sclerosis, Alzheimer's disease and primary immune deficiency. In February, the company started Phase II clinical trials following FDA review of its IND for Octagam 10% in mild-to-moderate Alzheimer's disease. ❖

Medicine

FDA Approves Novartis' New Seasonal Flu Vaccine

Accelerated approval has been granted by the U.S. Food and Drug Administration for Novartis AG's Agriflu to prevent disease caused by influenza virus subtypes A and B in adults ages 18 years and older. Because of the accelerated approval, Novartis is required to conduct additional studies to verify that Agriflu induces levels of antibodies in the blood that are effective in preventing seasonal flu.

The vaccine will be available in single-dose, prefilled syringes that do not contain preservatives. The FDA noted that Agriflu is not intended to protect against the 2009 H1N1 influenza.

The Swiss drugmaker also markets another seasonal influenza vaccine in the U.S., Fluvirin, which is approved for people ages 4 years and older. ❖

Supplier

Merck Now Exclusive Distributor of Afluria

Merck & Co., Inc. has entered into an exclusive agreement with CSL Biotherapies, a subsidiary of CSL Limited, to market and distribute Afluria, CSL's seasonal influenza vaccine, in the U.S., for the 2010-2011 through 2015-2016 flu seasons. Under the terms of the agreement, Merck will assume responsibility for all aspects of commercialization of Afluria in the U.S. CSL will supply Afluria to Merck and will retain responsibility for marketing the vaccine outside the U.S. Afluria was approved by the U.S. Food and Drug Administration in September 2007. It is indicated for the active immunization of persons age 6 months and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.

With the addition of seasonal flu vaccine, Merck will market eight of the 10 vaccines on the recommended immunization schedule for adults in the U.S. CSL and Merck have been partners in vaccine development and marketing since 1980. ❖

Did You Know?

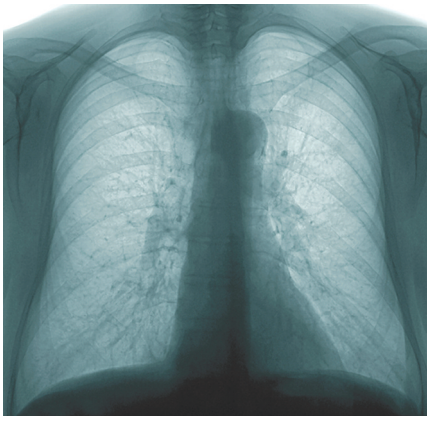
"Since 1988, when the Global Polio Eradication Initiative was established, the incidence of polio has decreased from an estimated 350,000 cases annually to 1,655 reported in 2008."

— Centers for Disease Control Morbidity and Mortality Weekly Report, April 3, 2009

Healthcare

Pneumonia Vaccine Could Prevent Flu Deaths

Because the serious consequences linked to the flu virus are the result of pneumonia, public health authorities are urging individuals to get the pneumonia vaccine to reduce hospitalizations and deaths associated with the virus. The Pneumovax vaccine, made by Merck & Co., stimulates the body's ability to neutralize the bacteria responsible for many cases of pneumonia. Preliminary reports presented to the Centers for Disease Control and Prevention (CDC) vaccine committee in June by Dr. Matthew Moore, a CDC medical epidemiologist, indicated that about 40 percent of swine flu-related pneumonia had an unknown cause, and about 30 percent were caused by S. pneumoniae



(Pneumovax protects against S. pneumoniae). Based on these statistics, Pneumovax has the potential to prevent an estimated one-third of pneumonia deaths linked to H1N1 flu. In addition, the vaccine provides protection against pneumonia for up to 10 years, so one vaccination provides at least some safeguard not just this year, but for future flu seasons as well.

"We would certainly like to see the vaccine used more extensively," said Dr. William Schaffner, chairman of the preventive medicine department at Vanderbilt University School of Medicine and president-elect of the National Foundation for Infectious Diseases. Unfortunately, in the U.S., recommendations have largely gone unnoticed. However, in Europe, the number of individuals getting the vaccine has risen in response to recommendations. ❖

Healthcare

Flu-Free Mom Receives Excellence Award

The Flu-Free and a Mom-to-Be consumer education campaign received the 2009 Immunization Excellence Award for Best Corporate Campaign at the National Influenza Vaccine Summit's annual meeting on June 29. The award recognizes individuals and organizations who have made extraordinary contributions toward improving influenza vaccination rates within their communities.

Developed by the National Women's Health Resource Center and the Association of Women Health, Obstetric and Neonatal Nurses, the Flu-Free and a Mom-to-Be campaign was created to protect moms-to-be and their babies, who are at high-risk, healthwise, during flu season. The message explains why it's safe for pregnant women to get the flu shot and how it can help them to avoid dangerous complications. Launched in October 2008, the campaign was made possible through an education grant provided by CSL Biotherapies. As of this writing, the campaign has reached more than 82 million individuals via print, online and broadcast outlets, and nearly 30,000 healthcare professionals and patients have been reached via direct mail distribution.

To access the Flu-Free and a Mom-to-Be program, go to www.healthywomen.org or www.awhonn.org. A CD titled "Home of the Flu Fighters," which includes sample materials from the campaign, can be requested by email at flufree@cslbiotherapies.com. ❖

Medicine

RiaSTAP Approved for Bleeding Disorder

RiaSTAP, the first and only treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia, has been approved by the U.S. Food and Drug Administration. RiaSTAP is a purified fibrinogen concentrate that undergoes virus inactivation and removal for safety assurance, and more than one million units have been sold worldwide. RiaSTAP is not indicated to treat dysfibrinogenemia.

Congenital fibrinogen deficiency is a rare, potentially life-threatening bleeding disorder that affects an estimated one person per million, with an estimated prevalence in the U.S. of approximately 300 patients. Fibrinogen, also called Factor 1, is a protein needed to form a blood clot. Fibrinogen levels in plasma determine the potential clotting ability and activity in the body. Diminished concentrations of fibrinogen limit the body's ability to form a clot. ❖

Healthcare

BayCuff Empowers Hemophilia Youth

The BayCuff self-infusion training program is an educational intiative designed to make infusion of recombinant factor VIII easier for both patients with hemophilia A and their caregivers. The centerpiece of the program created by Bayer HealthCare is an adjustable cuff worn on the hand or arm that allows patients to practice the technique of self-injection without actually infusing themselves and helps caregivers learn to administer home infusions for others.

"The idea for BayCuff was the result of 10 years of working with boys with hemophilia A and their families," said Tessa Speller, RN, formerly of the Henry Ekert Hemophilia Centre, Royal Children's Hospital, Melbourne, Australia, and inventor of BayCuff. "For both parents and boys themselves, self-treatment brings the ultimate goal — independence. The BayCuff self-infusion training program allows them to address issues such as needle phobias, working with their non-dominant hand and using veins they have not used before. Materials are designed to incorporate basic, as well as more advanced information, so teaching can be adapted based on the child's level of understanding."

The program is being distributed

by Bayer Healthcare to healthcare providers, and is available to all patients at no cost. For additional information, go to www.kogenatefs.com. ❖

Legal

Prometheus Patent Argument Upheld

The U.S. Court of Appeals for the Federal Circuit has ruled a test for determining the proper dosage of drugs to treat autoimmune disease is patentable under federal law. A three-judge panel said a federal district court judge incorrectly dismissed an infringement claim filed by Prometheus Laboratories against Mayo Clinic's medical laboratory division.

Mayo, which has long used Prometheus' patented test for determining the correct dosage of thiopurine drugs, announced in 2005 that it would begin selling its own dosage test. Prometheus filed an infringement lawsuit, but Mayo argued that Prometheus' lab method was not patentable because it is a patient's metabolite levels (natural phenomena) that warn a doctor of the drug's efficacy, rather than the Prometheus method. Prometheus, on the other hand, argued that such interpretations of therapeutic and diagnostic methods would likely have a chilling effect on future medical discovery and that "adoption of the district court's reasoning would have the effect of eliminating all medical treatment and diagnostic patents, when future medical advances will depend on optimizing treatment based on genetic or other testing."

Judge Alan D. Lourie writing for the Federal Circuit agreed with Prometheus that the method causes "physical transformations" to the human body and, as such, it "cannot be unpatentable … simply because they proceed according to natural laws or occur within the human body." In addition, Lourie wrote that the methods of treatment claimed in the patients "squarely fall within the realm of patentable subject matter because they 'transform an article into a different state or thing,' and this transformation is 'central to the purpose of the claimed process.'" ❖

Did You Know?

The Myositis Association was awarded a $1.25 million grant for research through the Department of Defense to determine environmental causes of developing myositis in first responders and the military.

Medicine

FDA Approves Gammaplex

The U.S. Food and Drug Administration approved the marketing of Gammaplex, a ready-to-use 5% intravenous immune globulin (IVIG) product for the treatment of primary humoral immunodeficiency. Gammaplex will be supplied in single-use bottles containing 50, 100 or 200 mL of 5% IVIG. Manufactured by Bio Products Laboratory (BPL), U.K., Gammaplex is distributed in the U.S. exclusively by FFF Enterprises, Inc. ❖

Reimbursement FAQs: Immune Globulin

Some commonly held misunderstandings about reimbursement for immune globulin (IG) are clarified.

Is it advisable to change a diagnosis so Medicare will cover the treatment?

It is fraudulent to inappropriately use a diagnostic code to attain reimbursement. In the case of primary immune diseases, Medicare currently reimburses for five disease states, with common variable immunodeficiency (CVID) (code 279.06) being the most commonly used. Medicare Local Coverage Determinations (LCDs) establish how broadly a diagnostic code can be used to attain reimbursement. Therefore, one must pay close attention to the LCDs in their regions for clarification.

For instance, the following is wording from a LCD covering Florida. "An adequate response of the stereotypes tested should include a two- to three-fold increase in titers to at least 50 percent of the stereotypes. In rare instances when there is recurrent bacterial infection and normal IgG levels, this criterion will be considered adequate to confirm the diagnosis of CVID."

Code 279.06 (CVID) includes these diagnoses:

- Dysgammaglobulinemia: acquired, congenital, primary
- Hypogammaglobulinemia: acquired primary
- Hypogammaglobulinemia: congenital non-sex-linked
- Hypogammaglobulinemia: sporadic

Caution should be exercised, as misinterpretation of the wording could still result in claims not being paid.

Will Medicare reimburse a home infusion pharmacy (durable medical equipment provider) for any IG infusion costs that take place outside of the patient's home beyond the cost of IG?

There are five diagnoses covered by the DME regional carrier (Part B): 279.04, 279.05, 279.06, 279.12 and 279.2. While it is true Medicare Part B will pay for IG for these five diagnostic codes, unless the patient is certified homebound, Medicare Part B will not pay for the nursing. In addition, Medicare Part B will not pay for the supplies used for home intravenous infusions. Other diagnoses, such as multiple autoimmune diseases, organ transplants, chronic lymphocytic leukemia and more are covered under Medicare Part B if infused in a clinical setting. To check diagnoses covered by local coverage determinations, go to www.cms.hhs.gov/DeterminationProcess/04_LCDs.asp#TopOfPage.

What is the most common reimbursement error?

Incorrect, incomplete or improperly matched coding are the most common reasons for denials or delays in payments. Many pharmaceutical companies recognize this and often have a team of experts willing to help. Depending on the product, much of that information is readily available online. Keep in mind that all coding must match the therapy. For instance, intravenous immunoglobulin (IVIG) generally requires infusion services to administer the treatment. If the claim fails to have a corresponding procedure code or claim for infusion services, all claims related to the IG may be automatically kicked out of the computer system, thus generating a denial or delay in payment until supporting documentation is filed.

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Email cjimenez@fffenterprises.com or call 951 296-2500, ext.1363, for more details on how you can be a part of these complimentary teleconferences.

Does Medicare pay for intravenous immune globulin (IVIG) in a homecare setting?

Medicare does pay for IVIG in the homecare setting. However, patients' diagnoses will determine whether they are covered under Medicare Part B or Part D.

Patients with primary immune deficiency disease (PIDD) are covered under Medicare Part B, but only for the IVIG product itself and not for any nursing services or the medical equipment needed to deliver IVIG. It's important to note that patients may find it difficult to find a homecare provider than can serve them unless they have a secondary insurance policy, rather than Medigap, which is also known as a supplemental policy. A secondary insurance policy — a true insurance policy that usually is provided to a working spouse or through a retirement plan — should cover nursing services and medical equipment.

PIDD patients utilizing subcutaneous immune globulin (SCIG) will find it easier to get services in the home because reimbursement rates fall under the Durable Medical Equipment benefit since a pump is required for infusing. Therefore, reimbursement rates for SCIG are higher and more homecare providers are able to service patients. Even though this is the case, the route of IG administration should be decided based on what is best for the patient and not the reimbursement rate.

Patients with a diagnosis other than PIDD, such as chronic inflammatory demyelinating polyneuropathy (CIDP), myositis, myasthenia gravis and other diseases, may be able to receive homecare under Medicare Part D. Again, nursing services and supplies are not covered. However, because reimbursement rates are higher, some homecare providers are able to service Part D patients. And, while Part D reimbursement is more favorable than Part B, patients need to be sure that their disease is covered and that their brand of IVIG is on the provider's formulary.

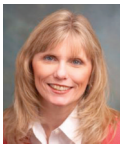
Will patients' IG be covered if they are on Medicare because of disability due to an autoimmune disease?

Many autoimmune diseases are covered under Medicare Part B, Medicare Advantage plans and Medicare Part D. Most diseases are off-label indications, but still fall under the standard of care. However, diseases such as myositis and myasthenia gravis may require that patients try other therapies before IVIG will be approved.

To receive IVIG under Part B, autoimmune disease patients must be treated in a clinical setting, because only patients with PIDD are covered in the home. Autoimmune disease patients have 80 percent coverage under Part B; the rest must be covered either through private insurance, a Medigap plan or a low-income subsidy qualification via state Medicaid. Unfortunately, about half of the states in the U.S. don't allow the disabled under 65 years of age to purchase Medigap plans. To find out if a state is one that allows supplemental coverage for the disabled, go to www.medicare.gov/medigap/under65.asp.

Disabled patients who do not qualify for low-income subsidies and who are unable to purchase a Medigap plan may want to consider an Advantage or Medicare Part C plan. These plans are similar to private insurance plans; they vary based on each disease in terms of how they are covered and at what percentage. Part C plans should cover at least what traditional Medicare Part A and B plans will cover. Some Part C plans will have higher premiums with lower copayments, while others will have low premiums with higher out-of-pocket expenses. When researching these options, it will be helpful for patients to have handy diagnostic codes, product codes and procedure codes for their treatment.

Regardless of which plan patients choose, getting coverage for therapy will depend on proper documentation from the physician before and after treatment is started. ❖



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

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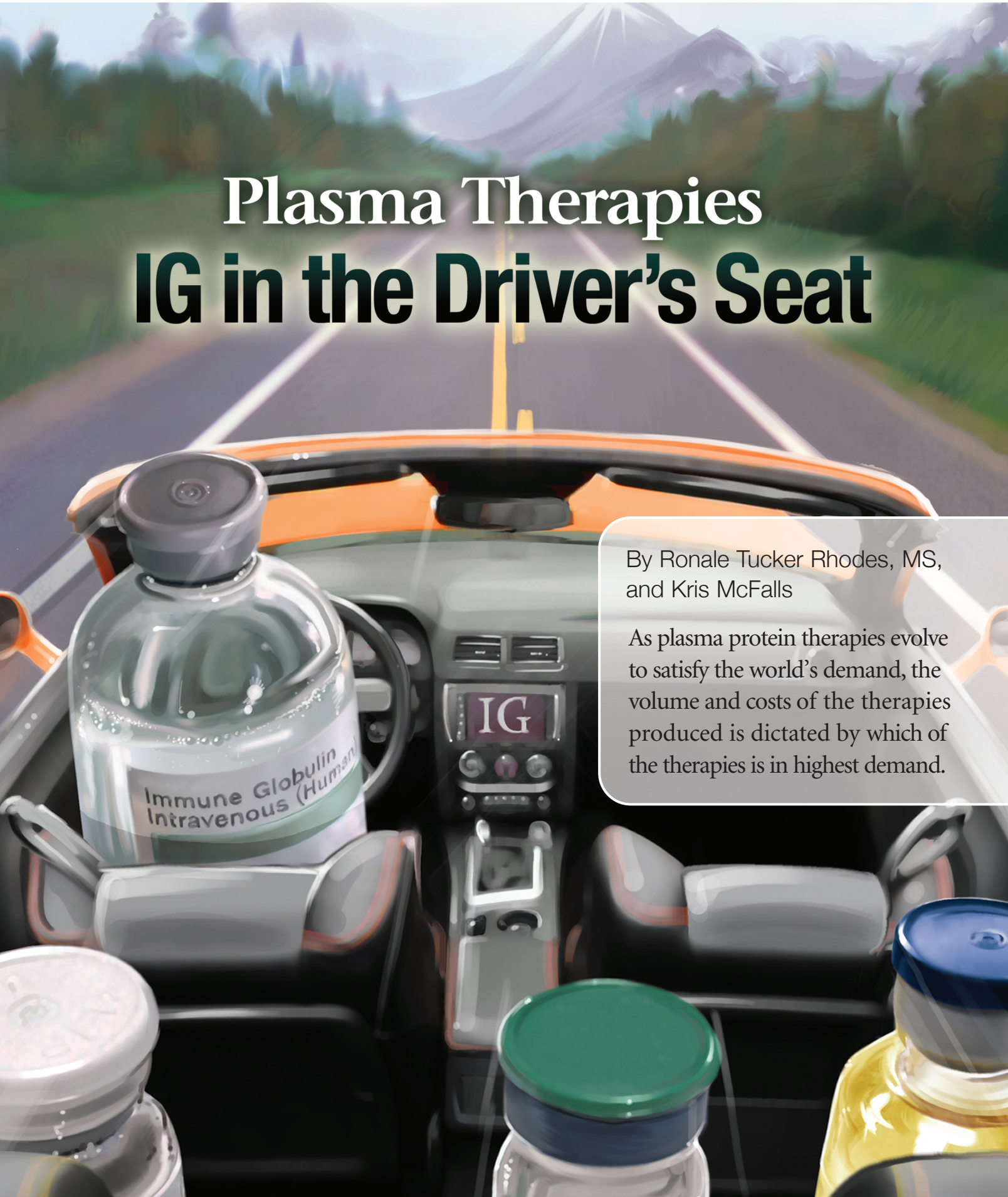
Plasma Therapies
IG in the Driver's Seat



By Ronale Tucker Rhodes, MS, and Kris McFalls

As plasma protein therapies evolve to satisfy the world's demand, the volume and costs of the therapies produced is dictated by which of the therapies is in highest demand.

The market for plasma protein therapies continues to offer lifesaving treatments for a growing number of individuals who suffer from a variety of diseases. Still, the intricacy of meeting the increasing demand for these therapies is often misunderstood. The reason is that manufacturing plasma protein therapies — how they are developed, in what quantities and at what cost — is perhaps one of the most perplexing production models because it differs significantly from traditional pharmaceutical manufacturing processes. Plasma pharmaceuticals rely solely on the proteins present in human blood, rather than on chemical processes that can be developed and/or improved for traditional pharmaceuticals. In further contrast, considerably fewer patients are treated with plasma products, and the cost of production is much higher due to the challenges of the manufacturing process.

The Facts of Plasma

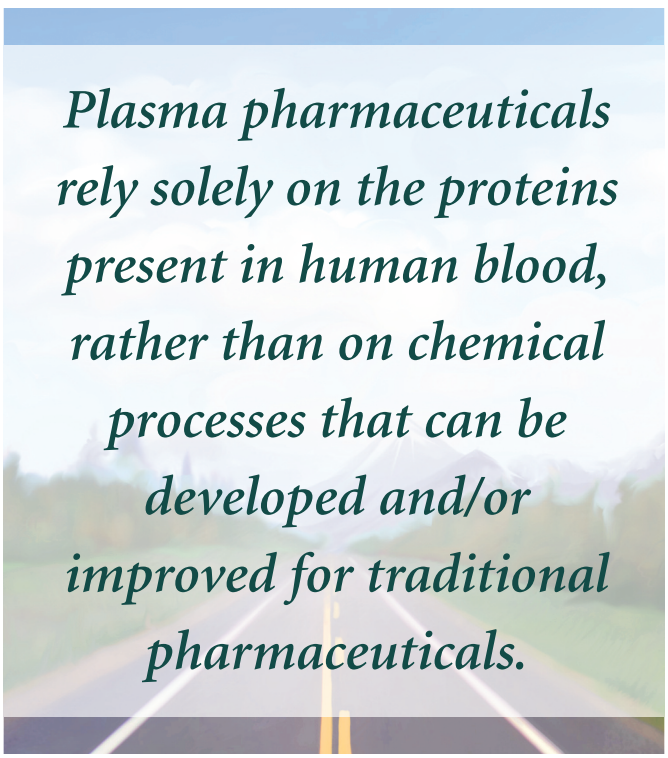
Most plasma is collected at the 380 U.S. Food and Drug Administration (FDA)-licensed and International Quality Plasma Program (IQPP)-certified plasma collection centers located throughout the United States.[1] The centers (owned almost exclusively by plasma therapy manufacturers) pay between approximately $15 and $40 for a donation of plasma, which, through a process known as plasmapheresis, is extracted as whole blood and then put into a centrifuge to separate the plasma. According to Patrick Robert, president of the Marketing Research Bureau Inc., an independent market research firm specializing in blood and plasma products, U.S. donors are the source of 47 percent of the world's plasma.

Worldwide, the total annual demand for plasma by pharmaceutical companies that manufacture plasma-based therapies is about 23 million to 28 million liters.[2] The amount collected by plasmapheresis in commercial plasma industry facilities is roughly 11 million liters from more than 15 million donations. And, the remaining liters are recovered from whole blood donations at community or American Red Cross (ARC) blood banks around the world.[3]

Once collected, plasma — 92 percent water and 8 percent proteins — must go through a fractionation process that separates and collects the individual proteins. According to Mary Kuhn, executive vice president of production at Talecris Biotherapeutics, of these proteins used to manufacture plasma pharmaceuticals, 64 percent are albumin, 20 percent are immune globulin, 2.5 percent are alpha-1 antitrypsin, less than 1 percent are clotting factors, and 13.5 percent are others, such as antithrombin, protein C, C1 esterase inhibitor, etc.

Fractionation: Making Therapies from Proteins

As part of the industry's voluntary international standards program for manufacturers, known as the Quality Standards of Excellence, Assurance and Leadership (QSEAL), all plasma is held in inventory for 60 days before it can enter the manufacturing process.[1] This allows for rigorous testing to identify, retrieve and destruct plasma donation from donors who are disqualified for various reasons, such as having received a tattoo or piercing at the time of the original donation or failing to report foreign travel.



Once the plasma is released from inventory, it is ready for fractionation. During the fractionation process, plasma is pooled from multiple donations, purified and processed in a specific order to extract specific plasma proteins that have a proven health benefit.[1] The steps and regulations required to collect donated plasma and complete the manufacturing process that ultimately results in the final therapies takes between seven and nine months. Between weeks 0 and 4, the plasma is collected. Then, between weeks 4 and 12, it is batched and transported to the fractionation plant, where it is stored from weeks 12 through 16. During this period, "it is the combination of time, temperature, pH and alcohol concentration

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)

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Solvent/Detergent Treated and Heated in Final Container at 80°C

BRIEF SUMMARY
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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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[that] allows the extraction of the specific therapeutic proteins."[1] At that point, the plasma is inspected and released for production. Production occurs between weeks 20 and 24. Then, between weeks 24 and 28, internal testing of the therapeutic proteins takes place, and the therapies are then released by the FDA and shipped between weeks 28 and 32 to the wholesalers and end users.

Manufacturing Costs of Plasma Therapies

The high cost of plasma, plasma testing and the lengthy production process boost the manufacturing costs for plasma protein therapies — much higher than chemical pharmaceuticals. Manufacturing costs for plasma products are about 65 percent of the price, compared with 20 percent to 25 percent for traditional pharmaceutical products.[4] And the costs have continued to rise due to changes in demand for therapies, new technologies and changes to regulatory measures introduced to improve the safety of plasma therapies.

Over the years, what has driven the amount of plasma collected — in order to meet the volume required for each therapy — has evolved. For instance, 30 years ago, the need for albumin determined how many liters of plasma were needed. Then, 20 years ago, it was the need for plasma-derived factor VIII. Today, the growing demand for immune globulin (IG) has put it in the driver's seat.[4]

With IG in highest demand, manufacturers have to produce greater amounts of the therapy, which results in proportionately greater amounts of the other protein therapies. For instance, the U.S. needs about 40 million grams of IG to treat patients with a variety of conditions. But, producing 40 million grams of IG results in about 250 million grams of albumin — far exceeding current demand. Fortunately, worldwide demand for albumin is increasing, particularly in China, Japan and Europe.

Further impacting the cost of production is regulation. Since the 1980s, the national and international "agencies regulating the plasma fractionation industry have developed a comprehensive set of measures to ensure the viral safety of plasma products."[2] These include multiple levels of regulatory oversight to ensure overlapping safeguards against the risks of transmitting blood-borne infectious agents. However, these rigid regulations, combined with the complex changes in technology to ensure the greatest progress in product purity and quality, have resulted in decreased yield for most proteins, apart from albumin.

Manufacturers, in turn, have expended substantial research and technology investments to increase the yield and to identify additional enhancements that can create even more effective therapies.[1]

A Promising Outlook for Plasma

While the process of manufacturing plasma protein therapies is complex, patients have benefited greatly. Not only are there more therapies to treat diseases, but these therapies are also safer than ever before.

But today's promising outlook doesn't alleviate the need for improvements. Despite strides in regulations, "regulatory disharmonies exist in the areas of donor acceptance, testing, Good Manufacturing Practices-related issues, batch release, documentation, clinical trial requirements and probably more."[4] By better harmonizing regulatory issues, the costs of production could be lowered and supply could be increased. In addition, discovering new uses for excess product and developing new therapies derived from plasma proteins with still unknown functions could also reduce manufacturing costs. ❖

RONALE TUCKER RHODES, *MS, is the editor of* BioSupply Trends Quarterly *magazine.* **KRIS MCFALLS** *is the patient advocate for* IG Living *magazine, directed to patients who rely on immune globulin and to their caregivers.*

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Better by Design:
New Coagulation Products on the Horizon

Scientists around the world are working to improve upon and create new therapeutic options for hemophiliacs.

By Keith Berman, MPH, MBA

The prospects didn't look good for a male infant born in 1960 with severe hemophilia. There was nothing available to prevent terribly painful and debilitating "bleeds" into the joints and muscles. Active play, sports and other physical activities were out of the question. Without a concentrated and quickly available replacement therapy for his critical missing clotting factor, chances were that he — like those before him — would die by early adulthood from an uncontrolled internal hemorrhage. If he survived, he faced a lifetime of pain and crippling joint damage.

Less than five years later, that young boy's odds improved dramatically. He and his parents could thank an extraordinary series of scientific and technological advances that transformed hemophilia care, and with it the lives of thousands of people with hemophilia A and B. Because of these advances, early developing bleeds can be readily managed or prevented almost entirely by self-treatment at home, using safe, purified concentrates of factor VIII (for hemophilia A) or factor IX (for hemophilia B).

Today, the drive to improve hemophilia therapy remains in high gear. Some scientists continue to pursue gene therapy — the definitive but elusive "cure" for these conditions. But, meanwhile, other scientists in labs and hospitals throughout the world are hard at work designing, developing and testing new clotting proteins that promise to resolve important drawbacks that persist with our current therapeutic options.

Hemophilia Therapy: How Far We've Come

While factor VIII and IX and their role in the "coagulation cascade" had been described by the early 1960s, no one had figured out how to isolate and concentrate them from human plasma. Because these clotting factors are present in plasma at very low levels, hemophilia patients suffering serious bleeds often had to further endure potentially dangerous transfusions of large quantities of plasma to get enough of the deficient protein.

Then in 1964, a Stanford physiologist named Judith Pool discovered that slowly thawing fresh frozen plasma causes it to separate into layers — and the heaviest layer on the bottom is enriched about tenfold with active factor VIII and IX proteins. Almost overnight, this cryoprecipitate, or "cryo," prepared by blood banks became the first effective treatment for hemophilia A and B.

But cryo had a major downside. It had to be stored frozen and administered in a hospital setting equipped to deal with serious adverse reactions. The clotting factor content could vary considerably from one unit to the next. Plasma fractionators stepped in to solve these problems by pooling large numbers of donor plasma units and further refining the cryoprecipitation process to produce specific concentrates rich in factor VIII or factor IX. Their first products — freeze-dried in small vials and stable at refrigerated temperatures — were introduced in the mid-1960s.

The availability of a purified factor concentrate that could be stored in a refrigerator set the stage for the next great leap in hemophilia care. By the early 1970s, patients were self-infusing the clotting factor concentrate at home, work or school to manage a bleed as soon as possible after the first appearance of symptoms.

Aware that as little as 1 percent of the normal level of active circulating clotting factor is enough to support hemostasis, specialists in Europe tried regular frequent injections of these products in patients in an effort to prevent irreversible joint damage and other debilitating or potentially life-threatening bleeds. The efficacy of prophylactic treatment is now well-established, and it is considered optimal therapy for children and many adults with severe hemophilia A and B.

Other advances that followed in the 1980s and 1990s focused mainly on creating safer products that have all but eliminated the risk of contamination with hepatitis viruses or HIV. Today, hemophilia specialists and patients have the choice of highly purified clotting factors isolated from human plasma or produced synthetically using recombinant DNA technology.

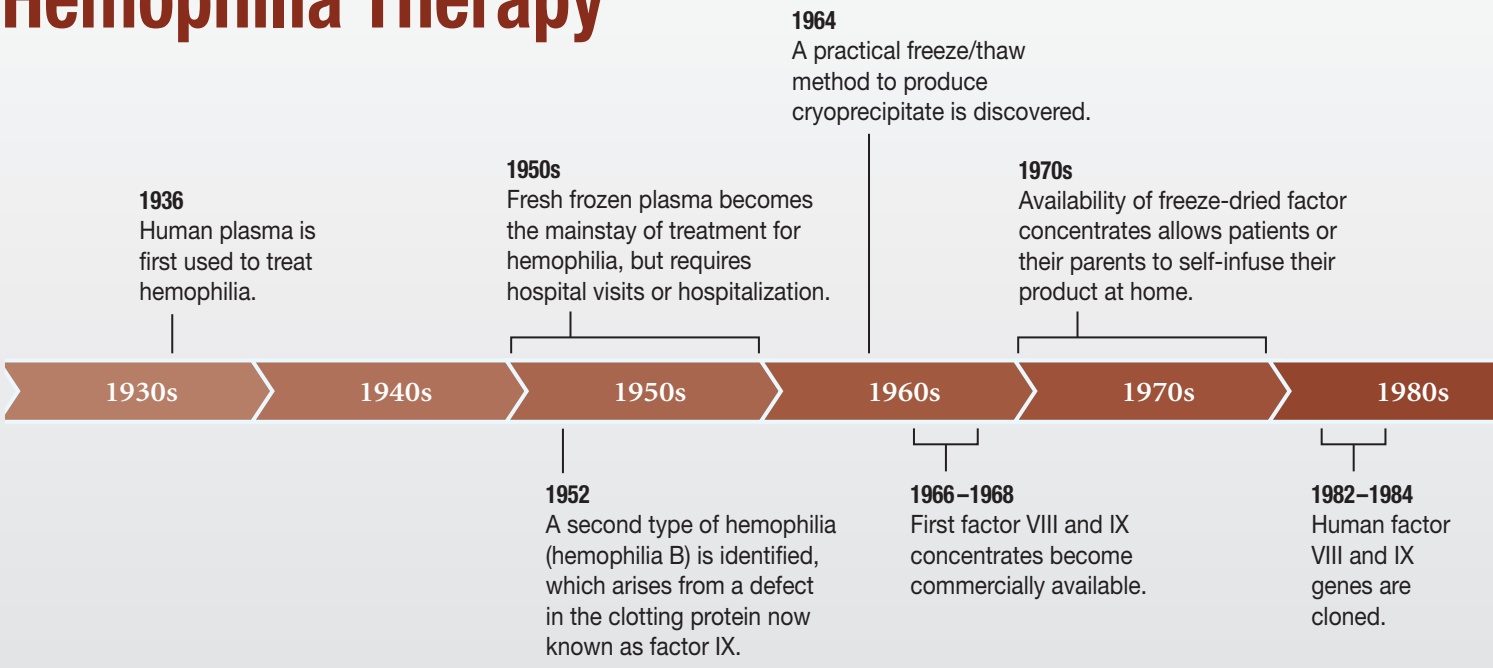
Today, the drive to improve hemophilia therapy remains in high gear.

With careful adherence to prescribing orders, people with even severe hemophilia can expect to live a normal life span with far less disability than in the era before today's highly purified factor concentrates. But problems and unmet needs remain in hemophilia therapy. Too many injections are required to prevent or control bleeds, which can be particularly challenging for younger children. The product doesn't work quickly enough. And, exposure to a new product sometimes triggers dangerous "inhibitor" antibodies that dramatically complicate treatment and increase its cost.

First Needs: Longer-Acting Coagulation Factors

Roughly half of people with hemophilia A and one-third of those with hemophilia B are classified as severe because of the negligible functional activity of their defective factor VIII or IX coagulation proteins.

Key Advances in Hemophilia Therapy



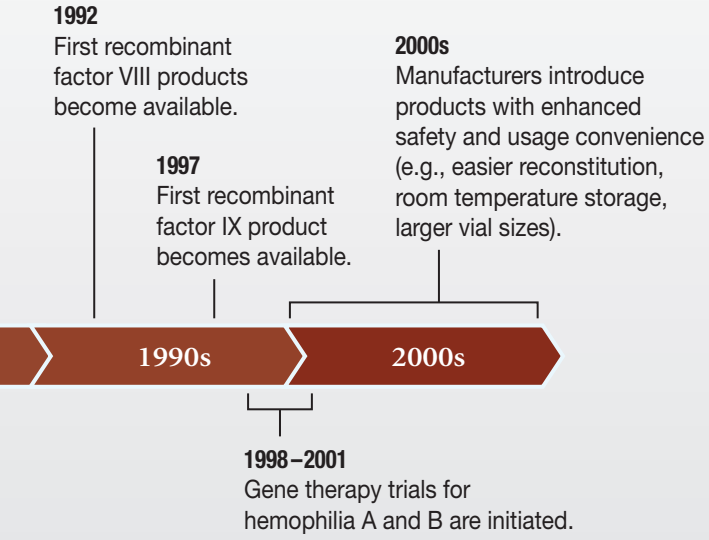
For children with severe hemophilia, prophylaxis — usually starting at under 1 or 2 years of age — is the optimal therapy to minimize the risks of acute life-threatening bleeds and long-term disability. Many severely affected adults also are prescribed regular prophylactic injections of clotting factor to reduce the frequency of bleeds and permanent damage to ankle, knee, elbow and other joints. And, hemophilia patients who use factor concentrates only "on demand" when they experience hemorrhages into joints or soft tissues also often require multiple, frequent infusions to manage their bleeds.

Yet many patients and their adult caregivers can't successfully manage multiple self-injections a week, or, in some cases, as often as every other day. In prophylaxis studies in children, noncompliance rates of up to 40 percent have been reported, with time and challenges of the infusions being the most common reasons. Similar problems also have been reported about adults who started on prophylaxis but later dropped out. While some resume prophylaxis after experiencing bleeds, others do not. In very young children for whom IV injections are especially challenging, a central venous access device is often implanted, adding risks of serious infection or thrombosis.

So why the need for so many injections in the first place? Very simply: The half-life of the injected factor — the amount of time for half of the injected protein to disappear from the circulation — is a mere 10 hours for factor VIII and less than 24 hours for factor IX.

Too many injections are required to prevent or control bleeds, which can be particularly challenging for younger children.

In response to this, a number of competitors are now well along in development of novel factor VIII and IX products manipulated in unique ways to prolong their circulating half-life:



• **Pegylation**. Novo Nordisk is now evaluating the safety of its "pegylated" recombinant factor IX (rFIX) in non-bleeding patients with hemophilia A. This concept of coating a therapeutic protein with a polyethylene glycol (PEG) has been proven to prolong the half-life of several biopharmaceuticals now licensed and available in the U.S. In a recent study in minipigs, Novo's pegylated factor IX had more than a fourfold longer half-life than a licensed rFIX.

Novo has separately reported a dramatically extended half-life for an experimental pegylated version of NovoSeven, its recombinant factor VIIa (rFVIIa) used as a "bypassing agent" in hemophilia patients with inhibitors who fail to respond to conventional clotting factors.

For hemophilia A patients on prophylaxis, Baxter Healthcare is developing long-acting rFVIII-von Willebrand factor products that may allow as little as a single weekly injection. They incorporate either a proprietary PEG reagent or a biodegradable polymer to extend circulating half-life.

• **Liposomal encapsulation**. Bayer Healthcare has found a way to encapsulate its Kogenate FS rFVIII in liposomes, which are microscopic spheric particles made of a lipid bilayer similar to a cell membrane. For good measure, they have pegylated these liposomes to further prolong the half-life of this rFVIII. A 260-patient Phase II study that started in June will determine whether once-a-week injections of the product for a full year are as effective at preventing bleeds in severe hemophilia A patients as a much higher total dose of Kogenate FS self-administered three times weekly.

• **Genetic modification**. By introducing gene mutations and other design changes, Bayer scientists also have produced an rFVIIa "analogue" that they report has a fivefold longer half-life than NovoSeven in hemophilic mice. Even more intriguing, better survival outcomes in a mouse bleeding model suggest that their "Bay7" rFVIIa might be more efficacious than NovoSeven as well.

• **Fc fusion technology**. Biogen Idec has genetically "fused" a recombinant factor IX molecule with the Fc portion of an antibody as a strategy to protect it from degradation and extend the time it remains in the circulation. The product is now in Phase II clinical trials, with a factor VIII version now being readied for human testing.

Better, Faster, Stealthier

Other innovative versions of factor VIIa, VIII and IX offer the promise of quicker initiation of clotting and improved efficacy over available versions. Work also is in progress on newly designed clotting proteins with reduced risk of triggering the patient's immune system to produce destructive inhibitor antibodies.

Octapharma, for example, has developed the first human cell line to express rFVIII, acting on the principle that the fully human cell-based production could yield an rFVIII protein variant with improved function and a reduced risk of immunogenicity. All other rFVIII products developed or approved to date are manufactured using animal cell lines. Functional assays and preclinical testing results appear very encouraging, according to the company.

Most of these prospective therapeutics are based on cutting-edge science; they will be in the research pipeline for at least several more years. But like their esteemed predecessors that have vastly changed the lives of thousands of people with hemophilia, those that deliver on their promise will be well worth the wait. ❖

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IVIG: At the Intersection of

During the past three decades, IVIG has proven an effective treatment for a wide range of autoimmune diseases, and it is now believed that IVIG may have clinical uses for a broader range of medical conditions.

By Keith Berman, MPH, MBA

It is an irony of nature that affects the lives of tens of millions of Americans. The ever-alert immune system that protects us against invading bacteria, viruses, foreign particles and cancerous cells can suddenly confuse "self" and "non-self" and turn its destructive forces on our own healthy body tissues.

This misdirected attack, known as autoimmune disease, can inflame or damage peripheral nerves, brain, muscle, skin, mucous membranes, blood vessels, joints, kidney, heart, gastrointestinal tract, cellular blood elements or multiple organs at the same time. Some autoimmune diseases more commonly affect one gender, race or age group. Sometimes they may be triggered by a recent acute viral infection. But more often, the underlying cause is unknown.

For many serious autoimmune disorders — such as rheumatoid and psoriatic arthritis, inflammatory bowel diseases and systemic lupus erythematosus — physicians prescribe corticosteroid therapy. Often, steroids will be combined with powerful small-molecule drugs developed originally for cancer therapy (e.g., cyclophosphamide, methotrexate and azothioprine) or with synthetic protein immunomodulators.[1]

But attempts to gain the upper hand through aggressive use of these immunosuppressive drugs usually come at a cost. Long-term corticosteroid therapy can result in such complications as diabetes, osteoporosis, formation of cataracts and aseptic necrosis of bone. Other immunosuppressive drugs may increase the risk of opportunistic infections, certain cancers or a host of other serious adverse events. And often, the disease simply fails to adequately respond.

All of these issues help to explain why, in the early 1980s, excellent clinical and safety findings using intravenous immunoglobulin (IVIG) in a difficult-to-treat autoimmune platelet disorder have been followed by literally hundreds of studies and case reports documenting its effects in a wide range of autoimmune diseases. The meandering path of IVIG clinical research recalls the insight of the great scientist Marie Curie a century ago: "The way of progress is neither swift nor easy." Three decades after IVIG was first licensed for clinical use, studies are just now underway to answer whether this powerful natural mediator of immune function can reduce death or disability in several of the most lethal and problematic diseases to afflict mankind.

1980: A Serendipitous Discovery in ITP

Some of the most important discoveries in medicine occur by chance and close observation. In 1980, Swiss physicians who administered IVIG to a child with congenital agammaglobulinemia who was also affected with immune thrombocytopenic purpura (ITP) were surprised to see his platelet counts increase sharply after administering IVIG. This team went on to successfully treat six children with acute ITP, with no untoward effects.[2] Shortly thereafter, U.S. and other investigators confirmed the platelet-boosting effect of IVIG in children and adults with chronic ITP who were unresponsive to corticosteroids or required high maintenance doses, again with no significant side effects.[3]

While scientists speculated about the mechanisms by which IVIG protects platelets from self-attack and destruction, this fortuitous discovery spurred physicians throughout the world to evaluate its effects in dozens of other unrelated autoimmune diseases. The resulting profusion of uncontrolled patient series, individual case reports and a relative handful of well-designed trials has been carefully sifted by clinical experts. Their meta-analyses, professional practice guidelines and insurance coverage policies collectively represent the current consensus that human autoimmune disorders clearly respond to IVIG therapy.

The Other Work of IgG Antibodies

On a separate track, immunologists set about trying to answer the larger question: When IVIG works, how exactly does it work? The answer begins by recognizing that only a small portion of the circulating and tissue-bound IgG antibodies in our bodies are directed against bacteria, viruses and other foreign agents to which we have been exposed in the past. The rest of our IgG has an immunomodulatory function. In a variety of ways, this IgG acts to regulate the potential for our immune system to mistake "us" for "them." Generally speaking, autoimmune diseases that respond to IVIG are thought to be those whose native IgG is overwhelmed or otherwise unable to adequately perform its immunomodulatory function. IVIG supplies the missing antibodies that go to work restoring part or all of that function.

The meandering path of IVIG clinical research recalls the insight of the great scientist Marie Curie a century ago: "The way of progress is neither swift nor easy."

In the instance of ITP, that natural regulatory function has gone awry. ITP patients produce antiplatelet antibodies that attach themselves to glycoproteins on the surface of their platelets. Coated with these abnormal antibodies, the platelets are quickly engulfed by macrophages and other phagocytes (literally "cells that eat") whose normal job is to clear bacteria and other invading pathogens. Included in IVIG prepared from large pools of donor plasma are specialized antibodies, called anti-idiotypic antibodies, that bind to and neutralize those antiplatelet antibodies. Other antibodies in IVIG appear to competitively block antibody receptors on macrophages, thus preventing them from engulfing healthy antiplatelet antibody-coated platelets.

Table 1. Autoimmune disorders for which IVIG is commonly prescribed

Autoimmune neuropathies
- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy

Neuromuscular junction defects
- Exacerbations of chronic severe myasthenia gravis
- Myasthenic crisis
- Lambert-Eaton myasthenic syndrome

Inflammatory myopathies
- Dermatomyositis
- Polymyositis

Autoimmune mucocutaneous blistering diseases
- Bullous pemphigoid
- Pemphigus vulgaris and pemphigus foliaceus
- Mucous membrane pemphigoid
- Epidermolysis bullosa acquisita

Others
- Kawasaki disease (acute vasculitis)
- Stiff-person syndrome (central nervous system disease)

Note: This is not an exhaustive list of all autoimmune disorders for which IVIG has demonstrated clinical benefit or which may be covered by health insurance plans. In addition, there are numerous autoimmune disorders for which IVIG has little or no discernible therapeutic benefit. The immune system derangements responsible for these conditions are largely outside the regulatory influence of IgG immunoglobulin.

Other autoimmune disorders for which IVIG is now often prescribed include autoimmune neuropathies, neuromuscular junction defects, inflammatory myopathies, mucocutaneous blistering disorders, a potentially life-threatening vasculitis and at least one central nervous system disorder (see Table 1).

Inflammatory Injury: The New Frontier for IVIG Research

It is now well appreciated, particularly in certain peripheral neuropathies (Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy) and inflammatory myopathies (dermatomyositis and polymyositis), that IVIG acts to rein in harmful inflammatory activity. Perhaps the most dramatic demonstration of this powerful IVIG anti-inflammatory effect is seen in Kawasaki disease. Symptoms of this acute childhood vasculitis include fever, rash, erythema of the lips and oral mucosa, and often development of potentially deadly coronary artery aneurysms. A single dose of IVIG in combination with high-dose aspirin promptly reduces fever and cuts the frequency of giant coronary artery aneurysms from 15 percent to 25 percent to around 1 percent.[4]

While IVIG is known to tamp down inappropriate inflammation in several ways, two in particular are now believed to have an outsized role:[5,6]

1. Cytokine regulation. IVIG modulates production of pro-inflammatory cytokines that attract and stimulate cytotoxic T cells, macrophages and other toxic inflammatory mediators, while upregulating anti-inflammatory cytokines.

2. Inhibition of the complement cascade. By interfering with inappropriate complement activation and scavenging active complement components, IVIG acts to prevent formation of the membrane attack complex (MAC) that directly causes tissue damage.

Just as the discovery of IVIG's effectiveness in ITP prompted researchers to test it in a wide array of autoimmune disorders, mounting evidence of its powerful anti-inflammatory function has spurred interest in evaluating how IVIG might affect the course of diseases where inflammation accounts for much, if not most, of the injury.

Now, after nearly three decades of clinical research that has established its therapeutic role in rare or little-known autoimmune diseases, ambitious new clinical studies are trying to answer whether IVIG can improve outcomes in other more common disorders that include a critical inflammatory component. Two of them — myocardial infarction (MI) and acute ischemic stroke — are all too familiar for the hundreds of thousands of people they continue to disable or kill every year.

IVIG for Acute Myocardial Infarction

The goal of the various coronary artery revascularization approaches in patients who survive a myocardial infarction is to preserve as much remaining healthy muscle in their ventricles as possible. Yet not everyone who suffers an MI is a candidate for revascularization. For those who are candidates, reperfusion may not only come too late but it can perversely contribute to a secondary inflammatory "reperfusion injury" to healthy heart muscle.

In an entirely new approach, Norwegian investigators are evaluating IVIG (Octagam, manufactured by Octapharma) in a double-blind placebo-controlled Phase III trial in patients who have experienced a myocardial infarction with resulting

CSL Behring

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 (s*ee 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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Based on June 2009 revision.

Table 2. IVIG immunomodulatory actions in certain disorders of autoimmunity

By studying its effects on other elements of the immune system, immunologists have described a number of ways that IVIG acts to modulate immune functions that directly or indirectly damage healthy cells and tissues.

Immunomodulatory actions of IVIG	Key mechanisms
Attenuates complement-mediated damage to normal or virus-infected cells	Prevents active complement fragments from binding to their specific receptors Prevents formation of the membrane attack complex (MAC) that directly destroys cells
Modulates pro-inflammatory cytokines	Rapidly reduces pro-inflammatory and induces anti-inflammatory cytokines; restores cytokine balance
Downregulates macrophage activity	Blockades Fc receptors on macrophages and other mononuclear phagocytes
Directly neutralizes autoantibodies	Binds anti-idiotypic IgG antibodies to self-directed autoantibodies
Interferes with autoantibody production	Downregulates maturation of autoreactive B cells and directs a complement-mediated cytotoxic effect on B cells and plasma cells secreting specific autoantibodies
Inhibits auto-reactive T cells	Interrupts interaction of T cells with antigen-presenting cells; alters T cell activation and differentiation

poor ventricular function. Pointing out that levels of certain pro-inflammatory cytokines are elevated during the first days following an MI, these researchers postulate that by broadly attenuating their expression, IVIG can reduce inflammation and resulting permanent damage to the left ventricle of the heart.[7] An earlier trial, by this same Oslo-based group, in patients with chronic heart failure showed that IVIG therapy induced a marked rise in plasma levels of certain anti-inflammatory cytokines, with a modest but statistically significant increase in left ventricular function.[8]

More recently, U.S. collaborators described a dramatic improvement in left ventricular ejection fraction (LVEF) in six patients with acute-onset inflammatory cardiomyopathy following treatment with high-dose IVIG (2 grams/kg). All had failed to respond to conventional therapy, and were referred for heart transplantation with a mean LVEF of less than 22 percent. At discharge, the mean LVEF had improved to just over 50 percent, with four of the six patients experiencing complete recovery. It remains to be seen whether these encouraging results in this rare non-ischemic myocarditis population bears any relevance to the potential for IVIG in MI patients, whose inflammatory response is the result of acute left ventricular ischemia.

IVIG for Neuropathic Pain

Neuropathic pain is very common, and all too commonly, this vexing problem is extremely difficult to manage. Such conditions as diabetic neuropathy, post-herpetic neuralgia and post-stroke pain affect as many as 3 percent of adults, many of whom cannot get adequate relief with their prescribed treatment.

Betting on its multiple anti-inflammatory effects, Canadian investigators are conducting a Phase II double-blind, saline-controlled cross-over trial to assess whether IVIG can subdue the neuroinflammation thought to be responsible for neuropathic pain. A dozen patients with moderate to severe treatment-resistant neuropathic pain will receive a divided dose of 2 grams/kg of IVIG (Gamunex, manufactured by Talecris Biotherapeutics) or a saline placebo infusion. Complete responders with prolonged relief will cross over to the alternative treatment when their pain returns, if this occurs within six months of treatment.

Separately, a German research team has just initiated a double-blind cross-over trial that will enroll 36 patients with complex regional pain syndrome, a frequent complication after limb trauma. They will receive three doses of IVIG (Gamunex) or a saline placebo every four weeks, followed by a washout period of three months, then the alternative treatment.

IVIG for Acute Ischemic Stroke

Stroke is among the three leading causes of death and the most important cause of permanent disability. In roughly 75 percent of cases, an acute ischemic event caused by blockage of a brain blood vessel is the immediate cause. But what immediately follows literally adds insult to injury: An inappropriate inflammatory response initiated by complement activation causes a second wave of structural damage and necrosis in surrounding ischemic brain tissues.

Hypothesizing that it might help mitigate stroke injury mediated by complement and other misguided immune functions,[9] a team led by National Institutes of Health investigators recently tested IVIG in an experimental mouse model of ischemic stroke.[10] Of 65 animals treated with a single infusion of IVIG 30 minutes before or three hours after stroke was induced, just one died. This contrasted with 13 deaths in the 66 animals that were infused with control reagents used to stabilize or suspend the IgG antibodies in IVIG.

Perhaps the most dramatic demonstration of this powerful IVIG anti-inflammatory effect is seen in Kawasaki disease.

Histological analyses matched well with these results. Ischemic brain sections of IVIG-treated mice revealed intact tissue architecture with only occasional neuronal loss, in contrast with edema, loss of architecture and extensive necrosis in the control groups. Surprisingly, a low dose of IVIG (0.5 grams/kg) was found to work about as well as a dose four times higher. There may be a neat explanation for this: Much of the systemically infused human IgG crossed the blood-brain barrier and accumulated at the site of the infarction, possibly attracted by harmful complement activation going on there.

Encouraging results like these must be tempered with an awareness that nearly every would-be therapy that reduced mortality and limited injury in small animal stroke models later failed to pan out in human studies. But unlike IVIG, none could lay claim to an established track record of effectiveness with excellent safety in human neurological and other inflammatory disorders. NIH investigators are currently in the early planning stages of a human stroke trial.

Looking Ahead

Clinical use of IVIG has evolved dramatically since immunologists 30 years ago confirmed its ability to provide protective antibody levels in primary immunodeficiency patients.[11] Today, thanks to hundreds of studies and case reports that followed, IVIG is routinely ordered by neurologists, rheumatologists, dermatologists, oncologists and transplant specialists.

But if past serves as prelude for this extraordinarily dynamic element of innate human immunity, the most exciting clinical discoveries with IVIG therapy may yet lie ahead. ❖

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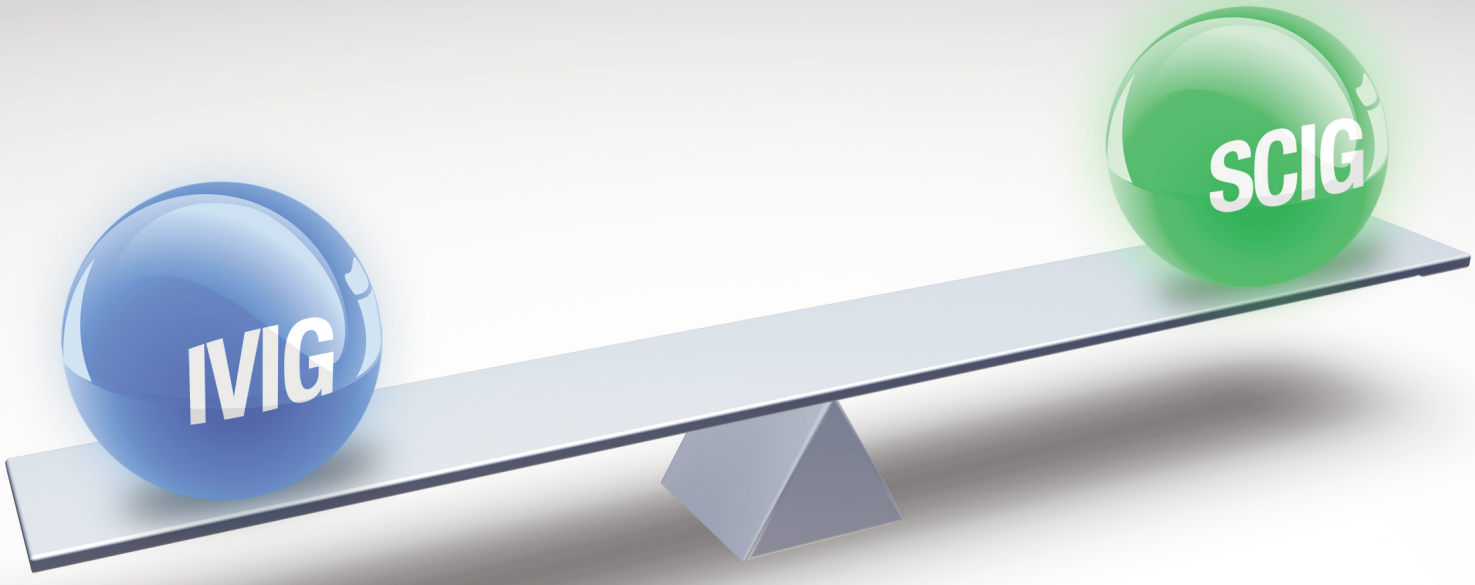

A Comparative Look at IVIG and SCIG

With the FDA approval of SCIG therapy in 2006, many patients now have the choice between SCIG and IVIG infusions. Understanding the differences between the two treatment modalities will help healthcare providers recommend the right one for their patients.

By Kris McFalls and Ronale Tucker Rhodes, MS

Prior to the early 1980s, most patients in need of immune globulin treatments had few options but to endure painful intramuscular injections, causing many to forgo therapy. And, while subcutaneous immune globulin (SCIG) infusions were being performed in the 1970s, they were not approved by the U.S. Food and Drug Administration (FDA), nor were they the norm. So, when intravenous immune globulin (IVIG) was licensed for use in the U.S. in 1981, it provided patients with a much-improved method of receiving their needed medication.

Almost three decades later, IVIG continues to be the primary treatment modality. For some, it is the therapy that works best for them; for others, it comes with complications, such as unwanted side effects and peripheral access problems, as well as the need for more convenient therapy. These issues led medical researchers to look back at the use of SCIG, and in 2006, the FDA approved the first SCIG product: CSL Behring's Vivaglobin.

But Vivaglobin is not the right product for every patient who requires IG infusions. As a result, many patients currently

infuse other IG products subcutaneously, despite the fact that the FDA has not given approval for that method of treatment. Knowing this, other manufacturers are testing new IG products for subcutaneous use. On the horizon are Baxter's Gammagard Liquid with recombinant human hyaluronidase currently in Phase III clinical trials, and Talecris' Gamunex awaiting FDA approval for a subcutaneous indication. Despite the product of choice, the question is whether SCIG or IVIG is best for patients, and that depends on many factors.

Cost of Product and Treatment

No significant differences in cost between SCIG and IVIG products exist either for the patient or insurer. However, there are different cost considerations related to the site of care, including nursing and supplies.

Protocol requires that all patients receive at least their first infusion in a clinical setting, whether infusing subcutaneously or intravenously.

The primary cost difference between the two types of treatment centers on supervision. During IVIG infusions, medical supervision is required, whereas it is not for SCIG patients who self-infuse and incur no infusion nursing costs. Even for IVIG patients, the cost to infuse at home is less than at a healthcare site. As a result, some insurance companies are encouraging both IVIG and SCIG patients to infuse at home rather than in a clinical setting. The exception to this is HMOs. Previously, HMOs had no outside costs for medical supervision in the clinical setting, so these organizations initially did not allow the transition to SCIG. But this is changing, and some HMOs are now starting to allow their patients to switch to SCIG.

Many IVIG patients prefer home treatment because it's more convenient for them since it cuts down on the cost and time of traveling to a clinical setting. While Medicare Part B will pay for IVIG preparation in the home — but only for primary immune deficiency (PIDD) patients — it will not pay for nursing or supplies in the home unless the patient is certified as homebound. On the other hand, IVIG in the home can be covered under Medicare Part D for indications other than PIDD, but again, supplies and nursing are not covered. In this situation, IVIG reimbursement is typically higher, so some homecare companies will often bundle the cost of nursing with the cost of the IVIG product if the reimbursement rate is high enough. In addition, many HMOs don't allow for IVIG home therapy because they are not set up to accommodate it, and as was previously noted, there are no outside costs for medical supervision in the clinical setting.

Overall, SCIG therapy in the home setting has a more favorable reimbursement rate than IVIG therapy. And, Medicare covers SCIG under the durable medical equipment (DME) benefit because, under the FDA approval, SCIG requires the use of a mechanical pump.

Comparing the Site of Care

Protocol requires that all patients receive at least their first infusion in a clinical setting, whether infusing subcutaneously or intravenously. After that, SCIG patients can treat themselves in the privacy of their homes, which offers convenience, autonomy and flexibility not found in the clinical setting. IVIG patients also have a choice. They can be treated in a clinic, hospital, outpatient infusion clinic and even in their home.

However, because IVIG requires monitoring by either an infusion nurse or doctor, these choices may be limited for some. Many patients can be infused safely at home, while others and their doctors may prefer the higher level of safety in a hospital or clinical setting — especially for patients at high risk of anaphylactic reaction or other issues such as myocardial infarction, brittle asthma, renal disease, etc., says Dr. Terry Harville, medical director at the Special Immunology Laboratory at the University of Arkansas for Medical Sciences. In addition, some patients have autoimmune conditions that require higher IVIG dosings than can be delivered subcutaneously, thus necessitating IVIG in a clinical setting.

Clinical infusions allow doctors and/or nurses to interact with patients on a monthly basis and provide a higher level of supervision for monitoring patients' overall health and response to treatment, which may be required for patients who are more likely to be noncompliant with therapy. For instance, many patients are so adept at living with chronic disease that they become anesthetized to symptoms that may be precursors of increased disease state or of oncoming infection. This desensitization, then, causes patients to sometimes fail to be good historians of their disease process, which can lead to

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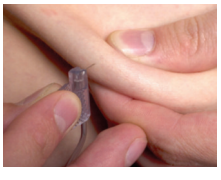


- Vivaglobin® Sub-Q treatment is injected into the thigh, upper arm, stomach or hips on a weekly basis
- Injection-site reactions are typically mild to moderate and decrease substantially over time

Vivaglobin®

Immune Globulin Subcutaneous (Human)

Important Safety Information

Immune Globulin Subcutaneous (Human), Vivaglobin®, is indicated for the treatment of patients with primary immunodeficiency (PI).

As with all immune globulin products, Vivaglobin® is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A deficiency who have known antibody against IgA. If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately and treat as medically appropriate.

Vivaglobin® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical trials, the most frequent adverse event was injection-site reaction, consisting of mild or moderate swelling, redness, and itching. No serious local site reactions were observed, and reactions tended to decrease substantially after repeated use. Other adverse events irrespective of causality included headache, gastrointestinal disorder, fever, nausea, sore throat, and rash.

As with all immune globulin (Ig) products, patients receiving Ig therapy for the first time, receiving a new product, or not having received Ig therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored in a clinical setting during the initial administration.

Ig administration can transiently impair the efficacy of live attenuated virus vaccines, such as measles, mumps and rubella.

In clinical studies, administration of Vivaglobin® has been shown to be safe and well tolerated in both adult and pediatric subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Safety and efficacy were not studied in pediatric subjects under two years of age.

Please see brief summary of Prescribing Information on adjacent page.

Manufacturing and Distribution:
Vivaglobin® is manufactured by CSL Behring GmbH and distributed by CSL Behring LLC.

1020 First Avenue • PO Box 61501
King of Prussia, PA 19406-0901 • USA
IO#9B046 12/2008

www.vivaglobin.com

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Vivaglobin®
Immune Globulin Subcutaneous (Human)

Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany
US License No. 1765

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

CSL Behring

℞ **only**

Before prescribing, please consult full prescribing information, a brief summary of which follows:

INDICATIONS AND USAGE
Vivaglobin® Immune Globulin Subcutaneous (Human), is indicated for the treatment of patients with primary immune deficiency (PID).

CONTRAINDICATIONS
As with all immune globulin products, Vivaglobin® Immune Globulin Subcutaneous (Human) is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency (serum IgA < 0.05 g/L) who have known antibody against IgA.

WARNINGS
Patients who receive immune globulin therapy for the first time, who are switched from another brand of immune globulin, or who have not received immune globulin therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored for these reactions in a clinical setting during the initial administration of Vivaglobin® Immune Globulin Subcutaneous (Human).

If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately. Treat any acute anaphylactoid reactions as medically appropriate.

Vivaglobin® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Vivaglobin® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such plasma-derived 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 manufacture (see **DESCRIPTION** section for virus reduction measures). Stringent procedures utilized at plasma collection centers, plasma-testing laboratories and fractionation facilities are designed to reduce the risk of virus transmission. The primary virus reduction steps of the Vivaglobin® manufacturing process are pasteurization (heat treatment of the aqueous solution at 60°C for 10 hours) and ethanol - fatty alcohol / pH precipitation. Additional purification procedures used in the manufacture of Vivaglobin® also potentially provide virus reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated. Any infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434 (in the US and Canada). The physician should discuss the risks and benefits of this product with the patient.

During clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin®.

PRECAUTIONS
General-Administer Vivaglobin® Immune Globulin Subcutaneous (Human), subcutaneously. **Do not administer this product intravenously.** The recommended infusion rate and amount per injection site stated under **DOSAGE AND ADMINISTRATION** should be followed. When initiating therapy with Vivaglobin®, patients should be monitored for any adverse events during and after the infusion.

Laboratory Tests - After injection of immunoglobulins, 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, D may cause a positive direct or indirect antiglobulin (Coombs') test.

Drug Interactions - Immunoglobulin administration can transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps and rubella. The immunizing physician should be informed of recent therapy with Vivaglobin® Immune Globulin Subcutaneous (Human), so that appropriate precautions can be taken.

Vivaglobin® should not be mixed with other medicinal products.

Pregnancy Category C - Animal reproduction studies have not been conducted with Vivaglobin® Immune Globulin Subcutaneous (Human). 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.

Pediatric Use - Vivaglobin® was evaluated in 6 children and 4 adolescents in the US and Canada study and in 16 children and 6 adolescents in the non-IND study. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Vivaglobin® was not studied in pediatric subjects under two years of age.

Geriatric Use - The clinical study of Vivaglobin® Immune Globulin Subcutaneous (Human), did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS
In clinical studies, administration of Vivaglobin® Immune Globulin Subcutaneous (Human), has been shown to be safe and well tolerated in both adult and pediatric subjects. Reactions similar to those reported with administration of other immune globulin products may also occur with Vivaglobin®. Rarely, immediate anaphylactoid and hypersensitivity reactions may occur. In exceptional cases, sensitization to IgA may result in an anaphylactic reaction (see **CONTRAINDICATIONS**).

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly, and appropriate treatment and supportive therapy should be administered.

In the US and Canada clinical study, the safety of Vivaglobin® was evaluated for 15 months (3-month wash-in/wash-out period followed by 12-month efficacy period) in 65 subjects with PID. The most frequent adverse reaction was local reaction at the injection site. Table 5 summarizes the most frequent adverse events by subject reported in the clinical study, and Table 6 summarizes the most frequent adverse events by infusion.

Table 5: Most Frequent Adverse Events by Subject *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 10% of subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	31 (48%)
Gastrointestinal disorder	24 (37%)
Fever	16 (25%)
Nausea	12 (18%)
Sore throat	11 (17%)
Rash	11 (17%)
Allergic reaction	7 (11%)
Pain	6.7 (10%)†
Diarrhea	6.7 (10%)†
Cough increased	6.7 (10%)†

*Excluding infections
† Due to missing subject diary information, values listed are estimates.

Table 6: Most Frequent Adverse Events by Infusion *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 1% of infusions) (Number of Infusions: 3656)	**No. of Adverse Events** (Rate**)
Adverse Events at the Injection Site	1789 (49%)
Mild	1112 (30%)
Moderate	601 (16%)
Severe	65 (2%)
Unknown Severity	11 (< 1%)
Non-Injection Site Reactions	
Headache	159 (4%)
Gastrointestinal disorder	40.3 (1%)†

*Excluding infections
**Rate = number of reactions/infusion
†Due to missing subject diary information, values listed are estimates.

Table 7 summarizes the most frequent related adverse events by subject reported in the clinical study, and Table 8 summarizes the most frequent related adverse events by infusion.

Table 7: Most Frequent Related Adverse Events by Subject* in the US and Canada Study

Related Adverse Event (≥ 2 subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	21 (32%)
Nausea	7 (11%)
Rash	4 (6%)
Asthenia	3 (5%)
Gastrointestinal disorder	3 (5%)
Fever	2 (3%)
Skin disorder	2 (3%)
Tachycardia	2 (3%)
Urine abnormality	2 (3%)

*Excluding infections

Table 8: Most Frequent Related Adverse Events by Infusion* in the US and Canada Study

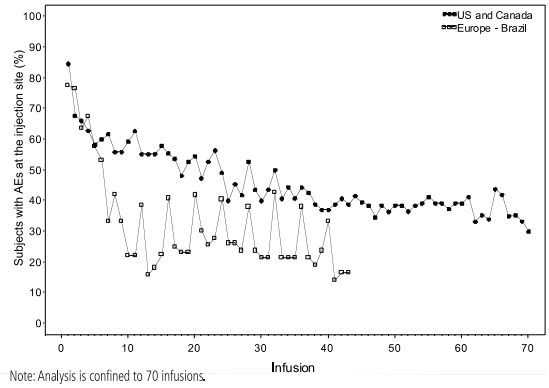
Related Adverse Event (≥ 2 AEs) (Number of Infusions: 3656)	**No. of AEs (Rate**)**
Adverse Events at the Injection Site	1787 (49%)
Non-Injection Site Reactions	
Headache	59 (1.6%)
Rash	9 (0.2%)
Nausea	9 (0.2%)
Nervousness	4 (0.1%)
Asthenia	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)
Skin disorder	3 (0.1%)
Urine abnormality	3 (0.1%)
Fever	2 (0.1%)
Dyspnea	2 (0.1%)
Gastrointestinal pain	2 (0.1%)
Tachycardia	2 (0.1%)

*Excluding infections
**Rate = number of reactions/infusion

In the non-IND Europe and Brazil clinical study, the safety of Immune Globulin Subcutaneous (Human), Vivaglobin® was evaluated for 10 months in 60 subjects with PID. The adverse events and their rates reported in this study were similar to those reported in the US and Canada study, with two notable exceptions for the related adverse events. These events were 59 episodes of headache (1.6%) and 2 episodes of fever (0.1%) in the US and Canada study and no episodes of headache and 18 episodes of fever (0.8%) in the Europe and Brazil study.

Local (Injection Site) Reactions - Local injection site reactions consisting of mostly mild or moderate swelling, redness and itching, have been observed with the use of Vivaglobin®. No serious local site reactions were observed. The majority of injection site reactions resolved within four days. Additionally, the number of subjects reporting local injection site reactions decreased substantially after repeated use (see Figure 1). Only three subjects in the US and Canada study and one subject in the Europe and Brazil study discontinued due to local site reactions.

Figure 1: Subjects Reporting Local Site Reactions By Infusion



Note: Analysis is confined to 70 infusions.

After administration, discard any unused solution and administration equipment in accordance with biohazard procedures.

HOW SUPPLIED
Vivaglobin® Immune Globulin Subcutaneous (Human), is supplied in single-use vials containing 160 mg IgG per mL. The following dosage forms are available:

NDC 0053-7596-03	Box of ten 3 mL vials
NDC 0053-7596-10	10 mL vial
NDC 0053-7596-15	Box of ten 10 mL vials
NDC 0053-7596-20	20 mL vial
NDC 0053-7596-25	Box of ten 20 mL vials

STORAGE
Store in the refrigerator at 2 - 8°C (36 - 46°F). Vivaglobin® Immune Globulin Subcutaneous (Human), is stable for the period indicated by the expiration date on its label. Do not freeze. Keep vials in storage box until use.

Based on April 2007 revision

less-than-optimal treatment. However, experienced infusion nurses who have monthly contact with patients can quickly spot subtle changes in patients' health. In turn, these nurses become skilled at asking questions that help the patients become better historians of their health status.

And while homecare offers many advantages to patients, there are other reasons why it may not be the best treatment or the treatment of choice. Compliance and the ability to perform SCIG treatments can be a concern, especially for younger individuals. And, there are those who prefer to keep their home a home — without the medical equipment as constant reminders of their disease. Many patients also prefer letting someone else take care of them for a while and like the comfort and safety they experience in a clinical setting.

Figures 1A and B. Serum Levels in 34-Year-Old Male with XLA

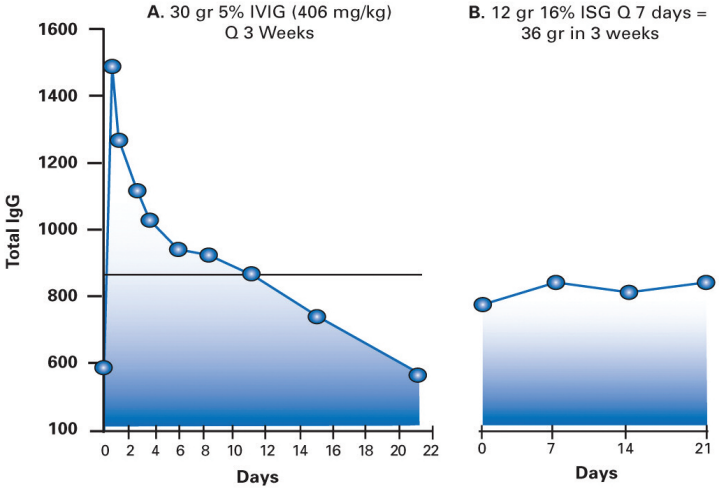
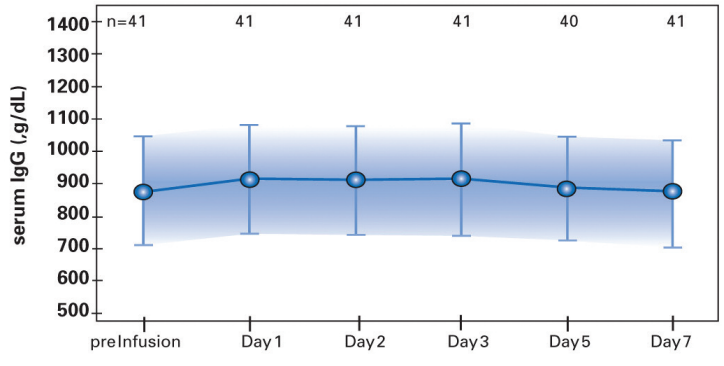


Figure 1C. Mean Serum IgG Levels Over Course of One Week During Steady-State Subcutaneous Therapy



Source: Immune Deficiency Foundation. *Clinical Focus on Primary Immune Deficiencies*. Issue 13, February 2008, p.2.

The primary cost difference between the two types of treatment centers on supervision.

Frequency of Treatment

Another distinction between the two treatments is the frequency of infusions. Typically, IVIG patients receive infusions every two to four weeks, whereas SCIG patients infuse every week. In fact, some SCIG patients are opting to infuse even more frequently. For instance, some doctors recommend patients give themselves one small daily injection instead of a single larger weekly infusion. Daily infusions are given by push, rather than with a pump. According to Dr. Hans Ochs, professor of pediatrics at the University of Washington, and a doctor at the Center for Immunity and Immunotherapies at Seattle Children's Research Institute, "Some adults dislike infusing with a pump and the infusion of large amounts of IG subcutaneously, but rather prefer to inject 10 to 12 mL [5 to 6 mL per site] daily, up to seven times per week. The advantage of giving IG by push several times a week is the simplicity of the procedures and the little time it takes [5 minutes or less]."

The frequency of IG treatments affects how patients feel, evidenced by their peak and trough levels. The level of IG in the bloodstream immediately after an infusion is known as the peak level; the level of IG right before the patient's next infusion is known as the trough level. Since IVIG patients receive fewer infusions spaced farther apart, they often experience increased lethargy due to low trough levels just prior to their scheduled infusion. In contrast, SCIG patients who have smaller and more frequent infusions experience higher and more stable trough levels with less variation between peak and trough. (See Figures 1A, B and C.) "There is very little change in IgG levels between the weekly infusions," explains Dr. Ochs. And, "there

Transitioning from IVIG to SCIG

Research has shown that patients who have received their first intravenous immunoglobulin (IVIG) infusions can safely transition to subcutaneous immunoglobulin (SCIG) therapy. While each individual's situation will need to be independently assessed, the following is one example of why and how a successful transition was made.

Margaret, a 77-year-old woman, was diagnosed with common variable immune deficiency nine years ago and began receiving monthly IVIG therapy. She has been pleased with her overall health since starting IVIG therapy. However, since she does not drive, she incurred additional cost for transportation to and from the infusion clinic. Her IVIG treatments caused frequent headaches and resulted in pain in both arms due to her "poor" veins, making it difficult for her to take care of herself at home. Although she received medication prior to infusions and the infusion rate was slowed, Margaret continued to experience adverse events. She was unhappy with the lengthy infusion time, side effects and travel costs.

Margaret has limited peripheral vascular access after episodes of inflammation of her veins (phlebitis). Because she is often mildly dehydrated, her veins tend to collapse upon venipuncture. She was recently diagnosed with type 2 diabetes, and is now taking an oral antidiabetic drug and following a restricted diet. Because of the adverse reactions, Margaret required professional observation during infusions. After complaining to her physician about the adverse reactions, the difficulty of accessing a vein for injection and the duration of IVIG therapy, Margaret learned about SCIG.

Since transitioning to SCIG, Margaret has not experienced any systemic adverse events. She has reported mild itching, redness and some swelling at the injection site, but these side effects decrease substantially within a day after the infusion. Margaret no longer requires professional observation of her therapy and is pleased with her ability to self-infuse at home on her own schedule. Because she is no longer distracted by the side effects she experienced with IVIG therapy, Margaret has been able to focus on managing her diabetes.

should be no fluctuation at all if the infusions are given several times a week."

In a 2003 survey by the Immune Deficiency Foundation, 68 percent of respondents indicated that they "usually" or "sometimes" could feel their IVIG "wearing off" before their next infusion was due. "The cause of this is not clear, but many doctors suspect this is due to increased symptoms from chronic infection [which may not otherwise be clinically apparent] and/or new infections occurring as the patient's IgG level drops," says Dr. Melvin Berger, division chief of allergy and immunology at University Hospitals Case Medical Center, and adjunct professor at Case Western Reserve University. "IgG in serum, no matter how it is infused, has an average half-life of about 22 days. This means that some people have shorter half-lives — their IgG gets used up by the body faster or is lost from the body via the kidneys or GI tract." Berger recommends that if patients experience an increased incidence of infections or increased symptoms near the time their next infusion is due, they discuss this with their doctor to determine whether their infusions should be given closer together and/or whether their dose should be increased.

"IgG given subcutaneously has the same half-life in the body as IgG given intraveneously, but it reaches its peak concentration more slowly — usually two to three days after it is given. In contrast, after an IV infusion, the peak is reached immediately," explains Berger. And, since in most subcutaneous treatment regimens, the next dose is given much sooner — often weekly or even twice a week or daily — the IgG is being replaced as soon as it is metabolized by the body, so the serum IgG level remains much more constant. "Several studies have documented that with subcutaneous infusions once a week, the serum IgG levels achieve nearly a true 'steady state,' eliminating many of the symptoms associated with the peaks and troughs of monthly IV infusions."

Safety Considerations

Regardless of whether patients are being treated with IVIG or SCIG, the risk of contaminated products is the same. All IG products must meet certain criteria established by the FDA for purity and safety. Yet, because IG is derived from human plasma, risk of potentially infectious agents cannot be totally eliminated. In the U.S., however, there has never been a documented case of HIV transmitted in IG.

IVIG patients, though, have a higher risk of thrombosis because infusion is administered through the vein. The risk is further heightened by a health history of diabetes, renal dysfunction, age (65 and older), coronary artery disease, hypertension, cerebrovascular disease, hyperviscosity disorder (including multiple myeloma, macroglobulinemia and polycythemia), thrombotic events and peripheral vascular disease. In addition, any patient who has had a vascular or cardiac

episode while receiving IVIG should be infused in a monitored setting. And, whenever a patient experiences an adverse reaction to IVIG, a new consent form must be completed.

Side Effects

Both IVIG and SCIG can cause manageable side effects, including headache, chills, nausea and flu-like symptoms. However, side effects do appear to be less severe for SCIG patients. Because SCIG is absorbed by the body more slowly through the fat tissue, instead of in large doses entered directly into the circulatory system, it is believed that SCIG causes milder systemic reactions than IVIG.

SCIG comes with site reactions, too, which usually decrease over time. These include mild-to-moderate swelling, itching, redness and tenderness at injection sites.

A Patient-by-Patient Decision

The inherent differences between IVIG and SCIG treatment modalities are significant. The determination to prescribe one over the other depends on each patient's unique situation, including their medical history, response to treatment, compliance with therapy and lifestyle. But, in general, Harville explains that "patients with difficult or more complicated disease would probably be better served in a clinical setting where an evaluation is performed with each monthly infusion. Patients with well-controlled disease capable of self-administration should probably be offered SCIG treatment at home." ❖

Transitioning from SCIG to IVIG

According to Dr. Terry Harville, medical director at the Special Immunology Laboratory at the University of Arkansas for Medical Sciences, compliance is one major concern when patients infuse in the home. This can be particularly true for younger patients who dislike the idea of infusions altogether. And, this was the case with one family whose sons required transitioning from SCIG back to IVIG to get them healthy again.

Darren and Christian Trump have combined variable immune deficiency (CVID). At ages 17 and 13, respectively, they decided to try switching to subcutaneous treatments in October 2006. According to their father, Gary, they had decided to try subcutaneous immune globulin (SCIG) because they felt that they were old enough to become independent. They also felt it would be easier and less risky since there would be less exposure to hospitals. In addition, statistics showed that it kept IG levels at a steadier rate, rather than the roller coaster up-and-down levels experienced with intravenous immune globulin (IVIG) treatments.

But SCIG didn't work — for either Darren or Christian. Although Gary tried to monitor the boys as well as he could, and the boys became proficient at inserting the subcutaneous needles, their trough levels dropped to very low levels. This was true for Darren more so than for Christian, because Christian doesn't have as serious a case of CVID. Why the trough levels dropped so low could have been a combination of several factors. For starters, compliance was an issue. Darren moved out of the house for a month and didn't infuse at all. In fact, his trough levels dropped as low as 369 (his normal range is between 645 and 1735). The boys are also very thin, which can make it harder to insert the needles, and Gary believes that it's possible that the boys may have needed higher levels of IG. No matter how hard they tried, after the drop in trough levels, Darren just couldn't catch up.

So, in April 2008 (just 14 months after switching to SCIG), the boys were transitioned back to IVIG. Today, at ages 20 and 16, the boys still prefer IVIG to SCIG. Darren prefers to make his own appointments and to go to the hospital. Gary takes Christian on Wednesdays. Both boys look forward to interacting with the pediatric staff that they've gotten to know during the past seven years, and when they're at the clinic, they enjoy watching TV and playing games.

Over the years, Gary says that the boys have tried four or five different products, they tolerate it well, and they've never really had a serious reaction. Today, Darren's trough levels are good, and this past June they were 851.

Suggested Resources

Vivaglobin:
www.vivaglobin.com/professional

Clinical Immunology Society:
www.clinimmsoc.org/teaching/index.php?cat=ivig&topic=immunoglobulin

KRIS MCFALLS *is the full-time patient advocate for* IG Living *magazine, written for patients who depend upon immune globulin products and their healthcare providers, and* **RONALE TUCKER RHODES**, *MS, is the editor of* BioSupply Trends Quarterly *magazine.*

Editor's Note: IG and IgG are common abbreviations with identical meaning, both referring to immune globulin.

Myths and Facts: MENINGITIS

While there is growing awareness about the seriousness of meningitis, there still exist a number of myths surrounding this sometimes deadly disease.

By Ronale Tucker Rhodes, MS

It's been called the silent killer because there are no obvious symptoms that would lead one to believe they have meningococcal meningitis. In fact, when victims first experience symptoms, they typically believe they have the flu. This often ignored and misunderstood disease strikes about 3,000 Americans each year and is responsible for approximately 300 to 360 deaths annually. About 20 percent of those who survive meningococcal disease suffer long-term consequences, such as brain damage, kidney disease, hearing loss or limb amputations.[1]

In the vast majority of cases, these are needless hospitalizations and deaths. Meningitis — the deadly form — can be prevented. All that is needed is to raise awareness of the seriousness of this disease, and dispel the myths surrounding it. Following are the most common myths about meningitis along with the facts to set the record straight.

Myth: Only one type of meningitis exists.

Fact: Two main types of meningitis exist: bacterial and viral. Bacterial meningitis, also known as meningococcal meningitis, is most commonly caused by one of three types of bacteria: Haemophilus influenzae type b (Hib), Neisseria meningitidis and Streptococcus pneumoniae. It is a serious infection of the fluid in the spinal cord and the fluid that surrounds the brain, and it can cause brain damage and even death.[2] Viral meningitis, the more common form, is also known as aseptic meningitis and is caused by any of a number of different viruses, many of which are associated with other diseases. This form of meningitis is a relatively common, but rarely serious infection of the fluid in the spinal cord and the fluid that surrounds the brain.[3]

Myth: Meningitis is a disease of the past now that there is a vaccine to prevent it.

Fact: While the number of cases of meningitis has declined since the introduction of a vaccine, it is still a serious disease that sickens, hospitalizes and kills. There are approximately 9,000 new cases of viral meningitis in America each year,[4] which normally occur as single, isolated events.[3] About 3,000 new cases of bacterial meningitis occur each year, responsible for between 300 and 360 deaths annually.[1] However, bacterial meningitis is relatively rare and usually occurs in isolated cases.[2]

Myth: Only children and teenagers can get meningitis. Healthy adolescents and young adults don't need to worry.

Fact: Anyone is at risk of contracting meningitis. Viral meningitis most often occurs in children and young adults.[3] The highest risk groups for bacterial meningitis are adolescents and preteens, college students and travelers.[5] People who have had close or prolonged contact with a patient with meningitis caused by Neisseria meningitidis or Hib can also be at increased risk. This includes people in the same household or daycare center, or anyone with direct contact with discharges from a meningitis patient's mouth or nose.[2] College students who live in dorms or group housing are at higher risk because of close contact and increased likelihood of sharing items, such as drinking glasses and utensils.[6]

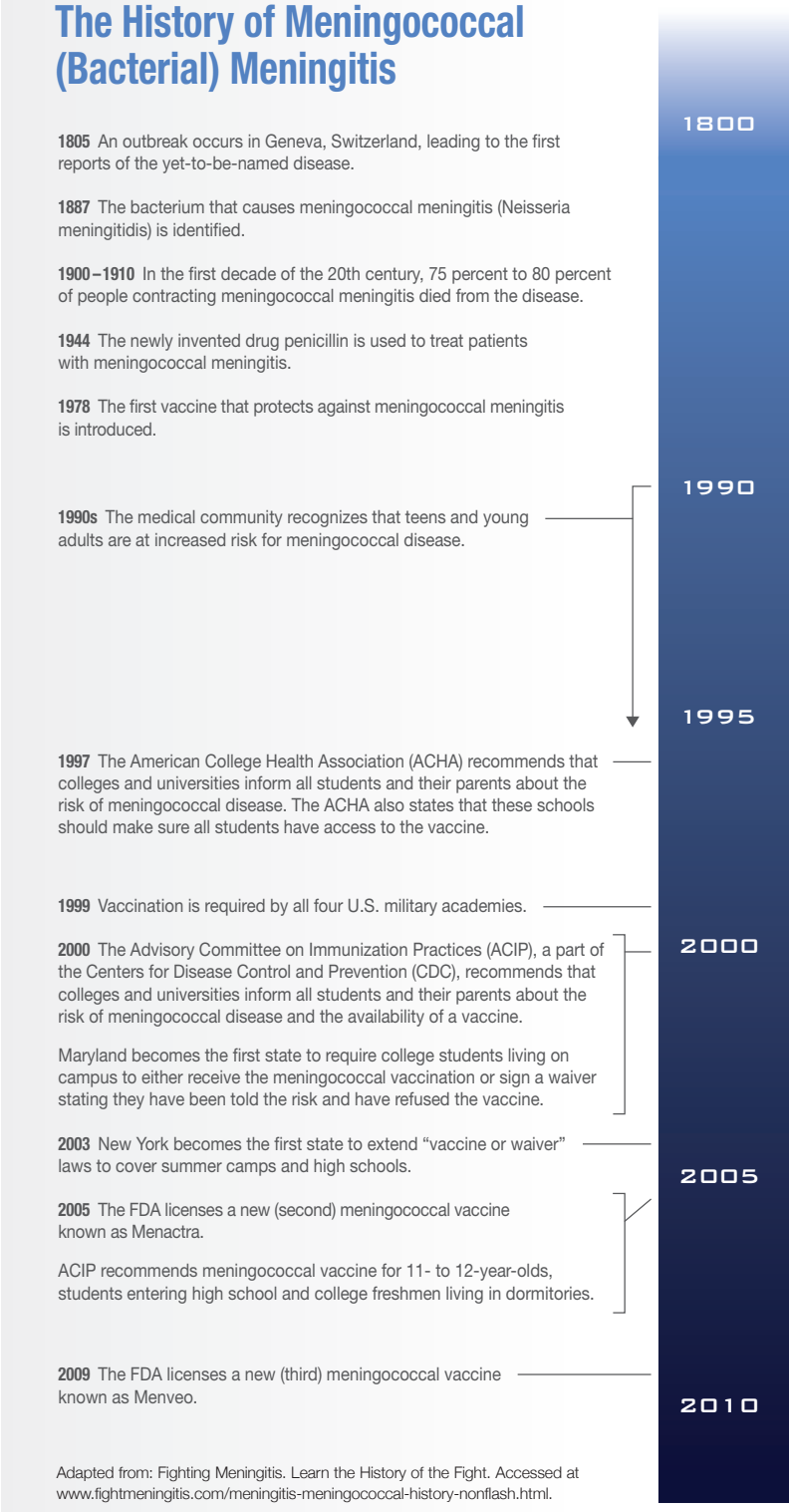
Myth: Meningitis is caused by casual contact with another person.

Fact: None of the bacteria that cause meningitis are very contagious, and they are not spread by casual contact or by simply breathing the air where a person with meningitis has been. Instead, the bacteria are spread by direct close contact with the discharges from the nose or throat of an infected person.[2] The spread of viral meningitis depends on the virus involved. Some viruses are spread by person-to-person contact; others are spread by insects, such as mosquitoes. And, very few people who become infected with these viruses actually develop meningitis.[3]

Myth: The symptoms of meningitis take a while to develop.

Fact: Viral meningitis symptoms include fever, chills, headache, abdominal pain, muscle pain, nausea and vomiting, drowsiness, confusion and abnormal sensitivity to light.[7] These symptoms generally appear within one week of exposure, are mild and typically clear up in less than 10 days.[3] Symptoms of bacterial meningitis develop quickly, usually between several hours and one to two days, and include high fever, nausea, severe headache,

The History of Meningococcal (Bacterial) Meningitis



Adapted from: Fighting Meningitis. Learn the History of the Fight. Accessed at www.fightmeningitis.com/meningitis-meningococcal-history-nonflash.html.

a stiff neck, vomiting, purple bruise-like areas, rash, sensitivity to light, mental status changes and a severe general ill feeling.[8]

Myth: It is easy to diagnose meningitis.

Fact: Bacterial meningitis is often misdiagnosed as something less serious because early symptoms are similar to influenza and other viral illnesses.[9] A physical examination will show a fast heart rate, low blood pressure, a stiff neck and a possible rash.[8] To diagnose both bacterial and viral meningitis, a lumbar puncture (spinal tap) needs to be performed to collect spinal fluid. Other tests could include a blood culture, CSF culture, CT scan of the brain, special strains of spinal fluid and white blood cell count.[7,8]

Myth: Meningitis will go away on its own.

Fact: Viral meningitis will go away on its own, but bacterial meningitis will not. In fact, bacterial meningitis must be treated early, or the risk of long-term complications, brain damage or death is possible. Once it is determined which strain of bacteria has been contracted, bacterial meningitis can be treated with a number of effective antibiotics.[7,8] Appropriate antibiotic treatment of most common types of bacterial meningitis should reduce the risk of dying from meningitis to below 15 percent, although the risk is higher among the elderly.[10]

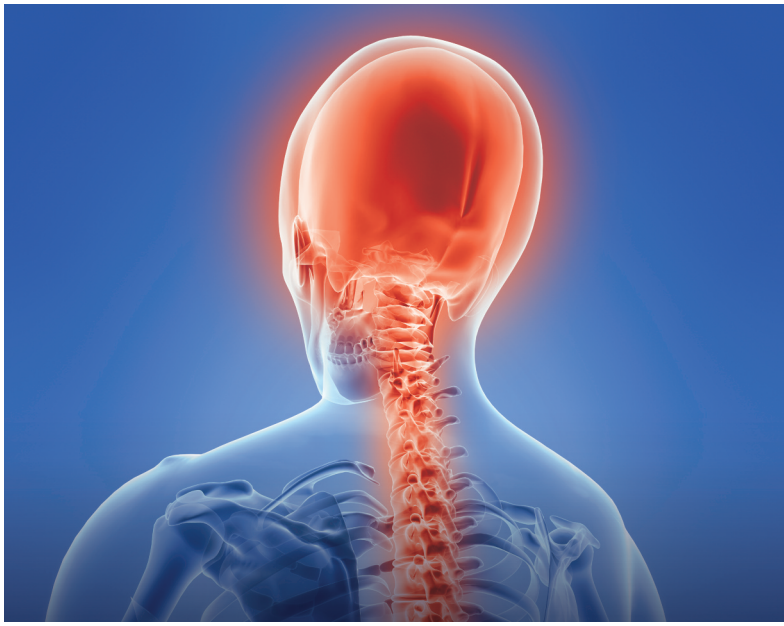
Myth: There is no way to prevent meningitis.

Fact: Individuals can reduce their risk of contracting both bacterial and viral meningitis. Bacterial meningitis can be prevented in most cases with vaccines. The Advisory Committee on Immunization Practices (ACIP) recommends all people ages 11 through 18 be vaccinated with one dose of MCV4, the meningococcal conjugate vaccine known as Menactra. ACIP also recommends college freshmen living in dormitories be vaccinated with

While the number of cases of meningitis has declined since the introduction of a vaccine, it is still a serious disease that sickens, hospitalizes and kills.

MCV4 before entering college, as well as people who have increased risk for meningococcal disease, if they have not previously been vaccinated.[10] MCV4 protects against Neisseria meningitides bacteria, as does a new vaccine called Menveo, which as of this writing, is expected to receive FDA approval by the end of 2009. Menveo is recommended for individuals ages 11 to 55.[11]

Two additional vaccines are available to protect against meningitis caused by the Streptococcus pneumoniae bacteria.



The pneumococcal polysaccharide vaccine PPV23 (Menomune) is recommended for all people ages 65 and older, as well as individuals at least 2 years old with certain chronic medical problems. The pneumococcal conjugate vaccine PCV7 is effective in infants to prevent pneumococcal infections and is routinely recommended for all children younger than 2 years old.[10] It is also recommended for children between 2 and 5 years old who have not already gotten the vaccine and are at high risk of serious pneumococcal disease.[12]

To protect against viral meningitis, individuals should pay particular attention to personal hygiene. Many of the viruses that cause viral meningitis can be prevented with handwashing. Hands should be washed with soap and warm water after using the toilet, after changing diapers, before preparing and eating food and after sneezing and coughing. In addition, individuals should avoid mosquito bites by staying inside between dusk and dark, when mosquitoes are most active. If outside, long pants and long-sleeved shirts should be worn, and insect repellent should be used.[3]

The CDC also notes that children can be protected against some diseases that can lead to viral meningitis by receiving their childhood vaccinations. These include vaccines against measles and mumps (the MMR vaccine) and chickenpox (the varicella-zoster vaccine).[10]

Myth: An individual can get sick from the meningitis vaccine.

Fact: The meningitis vaccine does not contain any live bacteria, so it is impossible to get meningococcal disease from the vaccination. Individuals may experience mild side effects that include redness or swelling at the site of injection that could last up to two days.

sanofi pasteur

The vaccines division of sanofi-aventis Group

Don't take a chance: You know the risks, but do your adolescent patients and their parents?

The ACIP[a] states the optimal time to immunize against meningococcal disease is 11–12 years of age, but all adolescents 11–18 years of age should be vaccinated.[1]

Only sanofi pasteur has almost 30 years' experience protecting against meningococcal disease — most recently with Menactra vaccine since 2005.

Take action with Menactra vaccine: Don't let any of your adolescent patients go unimmunized. Log onto www.vaccineshoppe.com or call 1-800-VACCINE (1-800-822-2463).

Indication

Menactra vaccine is indicated for active immunization against invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y, and W-135 in persons 2 through 55 years of age. Menactra vaccine will not stimulate protection against infection caused by *N meningitidis* other than serogroups A, C, Y, and W-135.

Safety Information

The most common local and systemic adverse reactions to Menactra vaccine include injection site pain, redness, and induration; headache, fatigue, and malaise. Other adverse reactions may occur. Menactra vaccine is contraindicated in persons with known hypersensitivity to any component of the vaccine or to latex, which is used in the vial stopper. Guillain-Barré syndrome (GBS) has been reported in temporal relationship following administration of Menactra vaccine. Persons previously diagnosed with GBS should not receive Menactra vaccine. Vaccination with Menactra vaccine may not protect all individuals.

Before administering Menactra vaccine, please see brief summary of full Prescribing Information on following page.

[a] ACIP = Advisory Committee on Immunization Practices.
[b] CPT = Current Procedural Terminology is a registered trademark of the American Medical Association.

Menactra vaccine is manufactured and distributed by Sanofi Pasteur Inc.

Reference: 1. Centers for Disease Control and Prevention. Notice to readers: revised recommendations of the Advisory Committee on Immunization Practices to vaccinate all persons aged 11–18 years with meningococcal conjugate vaccine. *MMWR.* 2007;56(31):794-795.

CPT®[b] Code: 90734

Menactra®
Meningococcal (Groups A,C,Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

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12/09 Printed in USA

Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine Menactra®

℞ only

FOR INTRAMUSCULAR INJECTION

Brief Summary: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE Menactra vaccine is indicated for active immunization of individuals 2 through 55 years of age for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y and W-135. Menactra vaccine is not indicated for the prevention of meningitis caused by other microorganisms or for the prevention of invasive meningococcal disease caused by *N meningitidis* serogroup B. Menactra vaccine is not indicated for treatment of meningococcal infections. Menactra vaccine is not indicated for immunization against diphtheria. Menactra vaccine may not protect all individuals.

CONTRAINDICATIONS Known hypersensitivity to any component of Menactra vaccine including diphtheria toxoid, or a life-threatening reaction after previous administration of a vaccine containing similar components,[1] are contraindications to vaccine administration. Known history of Guillain-Barré syndrome (see **WARNINGS** section) is a contraindication to vaccine administration. Known hypersensitivity to dry natural rubber latex (see **WARNINGS** section) is a contraindication to vaccine administration.

WARNINGS Guillain-Barré syndrome (GBS) has been reported in temporal relationship following administration of Menactra vaccine. An evaluation of post-marketing adverse events suggests a potential for an increased risk of GBS following Menactra vaccination[2] (see **ADVERSE REACTIONS, Post-Marketing Reports** section). Persons previously diagnosed with GBS should not receive Menactra vaccine. The stopper of the vial contains dry natural rubber latex, which may cause allergic reactions in latex-sensitive individuals. There is no latex in any component of the syringe. The ACIP has published guidelines for vaccination of persons with recent or acute illness (refer to www.cdc.gov).[3]

PRECAUTIONS General Before administration, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient's previous immunization history, the presence of any contraindications to immunization, the current health status, and history concerning possible sensitivity to the vaccine, similar vaccine, or to latex. As a precautionary measure, epinephrine injection (1:1000) and other appropriate agents and equipment must be immediately available in case of anaphylactic or serious allergic reactions. Special care should be taken to avoid injecting the vaccine subcutaneously since clinical studies have not been conducted to establish safety and efficacy of the vaccine using this route of administration. The immune response to Menactra vaccine administered to immunosuppressed persons has not been studied.

Information for Patients Prior to administration of Menactra vaccine, the health-care professional should inform the patient, parent, guardian, or other responsible adult of the potential benefits and risks to the patient (see **ADVERSE REACTIONS** and **WARNINGS** sections). Patients, parents or guardians should be instructed to report any suspected adverse reactions to their health-care professional. Females of childbearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy registry to monitor fetal outcomes of pregnant women exposed to Menactra vaccine. If they are pregnant or become aware they were pregnant at the time of Menactra vaccine immunization, they should contact their health-care professional or Sanofi Pasteur Inc. at 1-800-822-2463 (see **PRECAUTIONS** section).

Drug Interactions For information regarding concomitant administration of Menactra vaccine with other vaccines, refer to **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines.

Carcinogenesis, Mutagenesis, Impairment of Fertility Menactra vaccine has not been evaluated in animals for its carcinogenic or mutagenic potentials or for impairment of fertility.

Pregnancy Category C Animal reproduction studies have not been conducted with Menactra vaccine. It is also not known whether Menactra vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. There are no adequate and well controlled studies in pregnant women. Menactra vaccine should only be given to a pregnant woman if clearly needed. Assessment of the effects on animal reproduction has not been fully conducted with Menactra vaccine as effects on male fertility in animals has not been evaluated. The effect of Menactra vaccine on embryo-fetal and pre-weaning development was evaluated in one developmental toxicity study in mice. Animals were administered Menactra vaccine on Day 14 prior to gestation and during the period of organogenesis (gestation Day 6). The total dose given per time point was 0.1 mL/mouse via intramuscular injection (900 times the human dose, adjusted by body weight). There were no adverse effects on pregnancy, parturition, lactation or pre-weaning development noted in this study. Skeletal examinations revealed one fetus (1 of 234 examined) in the vaccine group with a cleft palate. None were observed in the concurrent control group (0 of 174 examined). There are no data that suggest that this isolated finding is vaccine related, and there were no vaccine related fetal malformations or other evidence of teratogenesis observed in this study. Health care providers are encouraged to register pregnant women who receive Menactra vaccine in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Menactra vaccine is administered to a nursing woman.

Pediatric Use Safety and effectiveness of Menactra vaccine in children below the age of 2 years have not been established.

Geriatric Use Safety and effectiveness of Menactra vaccine in adults older than 55 years have not been established.

ADVERSE REACTIONS The safety of Menactra vaccine was evaluated in 8 clinical studies that enrolled 10,057 participants aged 2–55 years who received Menactra vaccine and 5266 participants who received Menomune–A/C/Y/W-135 vaccine. There were no substantive differences in demographic characteristics between the vaccine groups. Among Menactra vaccine recipients of all ages, 24.0%, 16.2%, 40.4% and 19.4% were in the 2–10 year age range, 11–14, 15–25 and 26–55-year age groups, respectively. Among Menomune–A/C/Y/W-135 vaccine recipients of all ages, 42.3%, 9.3%, 30.0% and 18.5% were in the 2–10 year age range, 11–14, 15–25 and 26–55 year age groups, respectively. The three primary safety studies were randomized, active-controlled trials that enrolled participants 2–10 years of age (Menactra vaccine, N=1713; Menomune-A/C/Y/W-135 vaccine, N=1519), 11–18 years of age (Menactra vaccine, N=2270; Menomune–A/C/Y/W-135 vaccine, N=972) and 18–55 years of age (Menactra vaccine, N=1384; Menomune–A/C/Y/W-135 vaccine, N=1170), respectively. As the route of administration differed for the two vaccines (Menactra vaccine given intramuscularly, Menomune–A/C/Y/W-135 given subcutaneously), study personnel collecting the safety data differed from personnel administering the vaccine. Solicited local and systemic reactions were monitored daily for 7 days post-vaccination using a diary card. Participants were monitored for 28 days for unsolicited adverse events and for 6 months post-vaccination for visits to an emergency room, unexpected visits to an office physician, and serious adverse events. Unsolicited adverse event information was obtained either by telephone interview or at an interim clinic visit. Information regarding adverse events that occurred in the 6-month post-vaccination time period was obtained via a scripted telephone interview. At least 94% of participants from the three studies completed the 6-month follow-up evaluation. In the two concomitant vaccination studies with Menactra and either Typhim Vi or Td vaccines, local and systemic adverse events were monitored for 7 days post-vaccination using a diary card. Serious adverse events occurring within 1 month after each vaccination were reported and recorded.

Serious Adverse Events in All Safety Studies Serious adverse events reported within a 6-month time period following vaccination in children 2–10 years old occurred at the rate of 0.6% following Menactra vaccine and at a rate of 0.7% following Menomune-A/C/Y/W-135 vaccine. Serious adverse events reported within a 6-month time period following vaccination in adolescents and adults occurred at a rate of 1.0% following Menactra vaccine and at a rate of 1.3% following Menomune-A/C/Y/W-135 vaccine.

Solicited Adverse Events in the Primary Safety Studies The most frequently reported solicited local and systemic adverse reactions in US children aged 2–10 years (**TABLE 1**) were injection site pain and irritability. Diarrhea, drowsiness, and anorexia were also common. The most commonly reported solicited adverse reactions in adolescents, ages 11–18 years (**TABLE 2**), and adults, ages 18–55 years (**TABLE 3**), were local pain, headache and fatigue. Except for redness in adults, local reactions were more frequently reported after Menactra vaccination than after Menomune–A/C/Y/W-135 vaccination. The majority of local and systemic reactions following Menactra or Menomune–A/C/Y/W-135 vaccination were reported as mild in intensity. Between the vaccine groups, differences in rates of malaise, diarrhea, anorexia, vomiting, or rash, including urticaria, were not statistically significant.

Adverse Events in Concomitant Vaccine Studies

Local and Systemic Reactions when Given with Td Vaccine

The two vaccine groups reported similar frequencies of local pain, induration, redness and swelling at the Menactra injection site, as well as at the Td injection site. Pain was the most frequent local reaction reported at both the Menactra and Td injection sites. More participants experienced pain after Td vaccination than after Menactra vaccination (71% versus 53%). The majority (66%–77%) of local solicited reactions for both groups at either injection site were reported as mild and resolved within 3 days post-vaccination. The overall rate of systemic adverse events was higher when Menactra and Td vaccines were given concomitantly than when Menactra vaccine was administered 28 days after Td. In both groups, the most common reactions were headache (Menactra vaccine + Td, 36%; Td + Placebo, 34%; Menactra vaccine alone, 22%) and fatigue (Menactra vaccine + Td, 32%; Td + Placebo, 29%; Menactra vaccine alone,17%). Between the groups, differences in rates of malaise, diarrhea, anorexia, vomiting, or rash were not statistically significant. Fever ≥40.0ºC and seizures were not reported in either group.

TABLE 1: PERCENTAGE OF US PARTICIPANTS 2–10 YEARS OF AGE REPORTING SOLICITED ADVERSE REACTIONS WITHIN 7 DAYS FOLLOWING VACCINE ADMINISTRATION

	Menactra vaccine *N=1157			Menomune–A/C/Y/W-135 vaccine *N=1027		
Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Redness†	21.8	4.6	3.9	7.9	0.5	0.0
Swelling†	17.4	3.9	1.9	2.8	0.3	0.0
Induration†	18.9	3.4	1.4	4.2	0.6	0.0
Pain‡	45.0	4.9	0.3	26.1	2.5	0.0
Drowsiness§	10.8	2.7	0.3	11.2	2.5	0.5
Irritability‖	12.4	3.0	0.3	12.2	2.6	0.6
Arthralgia¶	6.8	0.5	0.2	5.3	0.7	0.0
Diarrhea#	11.1	2.1	0.2	11.8	2.5	0.3
Anorexia**	8.2	1.7	0.4	8.7	1.3	0.8
Fever††	5.2	1.7	0.3	5.2	1.7	0.2
Vomiting‡‡	3.0	0.7	0.3	2.7	0.7	0.6
Rash§§	3.4			3.0		
Seizure§§	0.0			0.0		

* N = The total number of subjects reporting at least one solicited reaction. The median age of participants was 6 years in both vaccine groups.; † Moderate: 1.0–2.0 inches, Severe: >2.0 inches; ‡ Moderate: interferes with normal activities, Severe: disabling, unwilling to move arm; § Moderate: interferes with normal activities, Severe: disabling, unwilling to engage in play or interact with others; ‖ Moderate: 1–3 hours duration, Severe: >3 hours duration; ¶ Moderate: Decreased range of motion due to pain or discomfort, Severe: unable to move major joints due to pain; # Moderate: 3–4 episodes, Severe: ≥5 episodes; ** Moderate: Skipped 2 meals, Severe: skipped ≥3 meals; †† Oral equivalent temperature; Moderate: 38.4–39.4°C, Severe: ≥39.5°C; ‡‡ Moderate: 2 episodes, Severe: ≥3 episodes; §§ These solicited adverse events were reported as present or absent only.

TABLE 2: PERCENTAGE OF PARTICIPANTS 11–18 YEARS OF AGE REPORTING SOLICITED ADVERSE REACTIONS WITHIN 7 DAYS FOLLOWING VACCINE ADMINISTRATION

	Menactra vaccine N*=2264			Menomune–A/C/Y/W-135 vaccine N*=970		
Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Redness‡	10.9†	1.6†	0.6†	5.7	0.4	0.0
Swelling‡	10.8†	1.9†	0.5†	3.6	0.3	0.0
Induration‡	15.7†	2.5†	0.3	5.2	0.5	0.0
Pain§	59.2†	12.8†	0.3	28.7	2.6	0.0
Headache‖	35.6†	9.6†	1.1	29.3	6.5	0.4
Fatigue‖	30.0†	7.5	1.1†	25.1	6.2	0.2
Malaise‖	21.9†	5.8†	1.1	16.8	3.4	0.4
Arthralgia‖	17.4†	3.6†	0.4	10.2	2.1	0.1
Diarrhea¶	12.0	1.6	0.3	10.2	1.3	0.0
Anorexia#	10.7†	2.0	0.3	7.7	1.1	0.2
Chills‖	7.0†	1.7†	0.2	3.5	0.4	0.1
Fever**	5.1†	0.6	0.0	3.0	0.3	0.1
Vomiting††	1.9	0.4	0.3	1.4	0.5	0.3
Rash‡‡	1.6			1.4		
Seizure‡‡	0.0			0.0		

* N = The number of subjects with available data; † Denotes $p < 0.05$ level of significance. The p values were calculated for each category and severity using Chi Square test; ‡ Moderate: 1.0–2.0 inches, Severe: >2.0 inches; § Moderate: Interferes with or limits usual arm movement, Severe: Disabling, unable to move arm; ‖ Moderate: Interferes with normal activities, Severe: Requiring bed rest; ¶ Moderate: 3–4 episodes, Severe: ≥5 episodes; # Moderate: Skipped 2 meals, Severe: Skipped ≥3 meals; ** Oral equivalent temperature; Moderate: 38.5–39.4°C, Severe: ≥39.5°C; †† Moderate: 2 episodes, Severe: ≥3 episodes; ‡‡ These solicited adverse events were reported as present or absent only.

TABLE 3: PERCENTAGE OF PARTICIPANTS 18–55 YEARS OF AGE REPORTING SOLICITED ADVERSE REACTIONS WITHIN 7 DAYS FOLLOWING VACCINE ADMINISTRATION

	Menactra vaccine N*=1371			Menomune–A/C/Y/W-135 vaccine N*=1159		
Reaction	**Any**	**Moderate**	**Severe**	**Any**	**Moderate**	**Severe**
Redness‡	14.4	2.9	1.1†	16.0	1.9	0.1
Swelling‡	12.6†	2.3†	0.9†	7.6	0.7	0.0
Induration‡	17.1†	3.4†	0.7†	11.0	1.0	0.0
Pain§	53.9†	11.3†	0.2	48.1	3.3	0.1
Headache‖	41.4	10.1	1.2	41.8	8.9	0.9
Fatigue‖	34.7	8.3	0.9	32.3	6.6	0.4
Malaise‖	23.6	6.6†	1.1	22.3	4.7	0.9
Arthralgia‖	19.8†	4.7†	0.3	16.0	2.6	0.1
Diarrhea¶	16.0	2.6	0.4	14.0	2.9	0.3
Anorexia#	11.8	2.3	0.4	9.9	1.6	0.4
Chills‖	9.7†	2.1†	0.6†	5.6	1.0	0.0
Fever**	1.5†	0.3	0.0	0.5	0.1	0.0
Vomiting††	2.3	0.4	0.2	1.5	0.2	0.4
Rash‡‡	1.4			0.8		
Seizure‡‡	0.0			0.0		

* N = The number of subjects with available data; † Denotes p <0.05 level of significance. The p values were calculated for each category and severity using Chi Square test; ‡ Moderate: 1.0–2.0 inches, Severe: >2.0 inches; § Moderate: Interferes with or limits usual arm movement, Severe: Disabling, unable to move arm; ‖ Moderate: Interferes with normal activities, Severe: Requiring bed rest; ¶ Moderate: 3–4 episodes, Severe: ≥5 episodes; # Moderate: Skipped 2 meals, Severe: Skipped ≥3 meals; ** Oral equivalent temperature; Moderate: 39.0–39.9°C, Severe: ≥40.0°C; †† Moderate: 2 episodes, Severe: ≥3 episodes; ‡‡ These solicited adverse events were reported as present or absent only.

Local and Systemic Reactions when Given with Typhim Vi Vaccine

The two vaccine groups reported similar frequencies of local pain, induration, redness and swelling at the Menactra injection site, as well as at the Typhim Vi injection site. Pain was the most frequent local reaction reported at both the Menactra and Typhim Vi injection sites. More participants experienced pain after Typhim Vi vaccination than after Menactra vaccination (76% versus 47%). The majority (70%–77%) of local solicited reactions for both groups at either injection site were reported as mild and resolved within 3 days post-vaccination. In both groups, the most common systemic reaction was headache (Menactra + Typhim Vi vaccine, 41%; Typhim Vi vaccine + Placebo, 42%; Menactra vaccine alone, 33%) and fatigue (Menactra + Typhim Vi vaccine, 38%; Typhim Vi vaccine + Placebo, 35%; Menactra vaccine alone, 27%). Between the groups, differences in rates of malaise, diarrhea, anorexia, or vomiting were not statistically significant. Fever ≥40.0ºC and seizures were not reported in either group.

Post-Marketing Reports The following adverse events have been reported during post-approval use of Menactra vaccine. Because these events were reported voluntarily from a population of uncertain size, it is not always possible to reliably calculate their frequency or to establish a causal relationship to Menactra vaccine exposure. Immune system disorders - Hypersensitivity reactions such as anaphylactic/anaphylactoid reaction, wheezing, difficulty breathing, upper airway swelling, urticaria, erythema, pruritus, hypotension. Nervous system disorders - Guillain-Barré syndrome, vasovagal syncope, facial palsy, transverse myelitis, acute disseminated encephalomyelitis. Musculoskeletal and connective tissue disorders - Myalgia.

DOSAGE AND ADMINISTRATION

Menactra vaccine should be administered as a single 0.5 mL injection by the **intramuscular** route, preferably in the deltoid region. Do not administer this product intravenously, subcutaneously, or intradermally. The need for, or timing of, a booster dose of Menactra vaccine has not yet been determined. Parenteral drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

Concomitant Administration with Other Vaccines

Safety and immunogenicity data are available on concomitant administration of Menactra vaccine with Typhim Vi, and Td vaccines (see **ADVERSE REACTIONS** section). Concomitant administration of Menactra vaccine with Td did not result in reduced tetanus, diphtheria or meningococcal antibody responses compared with Menactra vaccine administered 28 days after Td.[4] However, for meningococcal serogroups C, Y and W-135, bactericidal antibody titers (GMTs) and the proportion of participants with a 4-fold or greater rise in SBA-BR titer were higher when Menactra vaccine was given concomitantly with Td than when Menactra vaccine was given one month following Td. The clinical relevance of these findings has not been fully evaluated.[4] Concomitant administration of Menactra vaccine with Typhim Vi vaccine did not result in reduced antibody responses to any of the vaccine antigens.[4] The safety and immunogenicity of concomitant administration of Menactra vaccine with vaccines other than Typhim Vi or Td vaccines have not been determined. Menactra vaccine must not be mixed with any vaccine in the same syringe. Therefore, separate injection sites and different syringes should be used in case of concomitant administration.

STORAGE Store between 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product that has been exposed to freezing should not be used. Do not use after expiration date.

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Manufactured by:

Sanofi Pasteur Inc.
Swiftwater, PA 18370 USA
MKT16458

Product information
as of April 2008
Printed in USA
5665-5666

Myth: Getting a vaccine to prevent meningitis will protect individuals for life.

Fact: Menactra and Menveo provide at least eight years of protection, whereas Menomune lasts for around three to five years. Because the vaccines wear off, the CDC recommends individuals be vaccinated when they are exposed to a high-risk setting, such as moving into a college dormitory or traveling to Saudi Arabia or certain parts of Africa. Individuals who cannot afford the vaccine can call the CDC at (800) 232-4636 to find out where they can receive the vaccine for free or at a discounted price.[6] ❖

The highest risk groups for bacterial meningitis are adolescents and preteens, college students and travelers.

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

Flebogamma® 5% DIF

Immune Globulin Intravenous (Human)

Highly Purified IGIV

- Trace amounts of IgA: 0.0028 ± 0.0016 mg/mL[1]
- Appropriate for patients with restricted sodium intake
- Sorbitol stabilized, sucrose and maltose free

Demonstrated Benefits in Replacement Therapy

- In the pre-approval clinical trial[2]:
  - Only 0.021 serious bacterial infections/patient/year
  - None of the patients participating withdrew from the study due to a treatment-related adverse event

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- Seven validated viral elimination steps including:
  - 20 nm nanofiltration
  - Double specific inactivation
- Highly effective process:
  - 15.04 log reduction of PPV (B19 model virus)
  - ≥13.33 log reduction of EMCV (HAV model virus)

*Laser etched identifier number may at times be covered by the label.

(1) Mean value from 97 consecutive lots, data on file, Instituto Grifols, S.A.
(2) Berger M et al. A Multicenter, Prospective, Open Label, Historically Controlled Clinical Trial to Evaluate Efficacy and Safety in Primary Immunodeficiency Diseases (PID) Patients of Flebogamma 5% DIF, the Next Generation of Flebogamma. J Clin Immunol 2007;27:628-633.

For further information call **Grifols USA, LLC** Professional Service: 888-GRIFOLS (888-474-3657)
Customer Service: 888-325-8579 Fax: 323-441-7968 **www.grifols.com**

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Pure Confidence

Flebogamma® 5% DIF is indicated for replacement therapy in primary humoral immunodeficiency disorders

Important Safety Information

Immune Globulin Intravenous (Human) (IGIV) 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. Flebogamma® 5% DIF does not contain sucrose. See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Flebogamma® 5% DIF is made from human plasma. As with all plasma derived products, the risk of transmission of infectious agents, including viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated. Flebogamma® 5% DIF should not be administered to individuals with a history of severe or anaphylactic reactions to blood or blood-derived products. Patients with severe selective IgA deficiency (IgA < 0.05 g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction. Anaphylaxis can occur using Flebogamma® 5% DIF even though it contains low amounts of IgA (typically < 50 µg/mL). If patients are known to be intolerant to any component of Flebogamma® 5% DIF, such as sorbitol (i.e., intolerance to fructose), they should not receive the product. An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. AMS may occur more frequently in association with high-dose (e.g., > 1.0 g/kg body weight) and/or rapid-infusion IGIV treatment. Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. There have been reports of non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV. Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Reported adverse reactions with Flebogamma® 5% DIF and other IGIV products include: 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, often beginning within 60 minutes of the start of the infusion. Rarely, Immune Globulin Intravenous (Human) can induce a severe fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with IGIV. In the case of shock, the current standard medical treatment for shock should be implemented. **Please refer to adjacent Brief Summary of the Prescribing Information.**

FDA03-1-US-09

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Immune Globulin Intravenous (Human)
Flebogamma® 5% DIF
For intravenous use only
Rx only

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Flebogamma® 5% DIF is indicated for replacement therapy in primary (inherited) humoral immunodeficiency disorders.

DOSAGE AND ADMINISTRATION
The usual dose of Flebogamma® 5% DIF for replacement therapy in primary humoral immunodeficiency diseases is 300 to 600 mg/kg body weight administered every 3 to 4 weeks.

An in-line filter with a pore size of 15 to 20 microns is recommended for the infusion. Antibacterial filters (0.2 micron) may also be used. Discard unused contents and administration devices after use.

The infusion of Flebogamma® 5% DIF should be initiated at a rate of 0.01 mL/kg body weight/minute (0.5 mg/kg/minute). If, during the first 30 minutes, the patient does not experience any discomfort, the rate may be gradually increased to a maximum of 0.10 mL/kg/minute (5 mg/kg/minute).

For patients judged to be at risk for developing renal dysfunction or considered to be at increased risk of thombotic/thromboembolic events, it may be prudent to limit the infusion rate to a maximum rate less than 0.06 mL/kg body weight/minute (3 mg/kg/minute). Reduction in dose, concentration, and/or rate of infusion in patients at risk of acute renal failure, which includes patients over 65, has been proposed in the literature in order to reduce the risk of acute renal failure.

CONTRAINDICATIONS
Flebogamma® 5% DIF should not be administered to individuals with a history of severe or anaphylactic reactions to blood or blood-derived products. Patients with severe selective IgA deficiency (IgA < 0.05 g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction. Anaphylaxis can occur using Flebogamma® 5% DIF even though it contains low amounts of IgA (typically < 50 µg/mL). Such patients should only receive intravenous immune globulin with utmost caution and in a setting where supportive care is available for treating life-threatening reactions. If patients are known to be intolerant to any component of Flebogamma® 5% DIF, such as sorbitol (i.e., intolerance to fructose), they should not receive the product.

WARNINGS
Immune Globulin Intravenous (Human) (IGIV) 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. Flebogamma® 5% DIF does not contain sucrose.
See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Flebogamma® 5% DIF is made from human plasma. As with all plasma derived products, the risk of transmission of infectious agents, including viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated. The risk that such products will transmit an infectious agent has been greatly 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. 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 Grifols Biologicals at 888-GRIFOLS (888-474-3657).
All patients, but especially individuals receiving Flebogamma® 5% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at risk for the development of inflammatory reactions characterized by fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations may reduce the risk of these types of events.
Appropriate supportive care, including immediate access to epinephrine injection, should be available for the management of acute anaphylactic reactions.

PRECAUTIONS
General:
Any vial that has been entered should be used promptly. Partially used vials should be discarded and not saved for future use because the solution contains no preservative. Do not use if turbid. Solution that has been frozen should not be used.
Ensure that patients are not volume-depleted before the initiation of the infusion of IGIV.

Renal Function:
Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed before the initial infusion of Flebogamma® 5% DIF and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.
For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing Flebogamma® 5% DIF at a maximum rate less than 0.06 mL/kg (3 mg/kg) body weight/minute.

Aseptic Meningitis Syndrome:
An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. The syndrome usually begins within several hours to 2 days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic milliliter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high-dose (e.g., > 1.0 g/kg body weight) and/or rapid-infusion IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis:
Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration [See ADVERSE REACTIONS]. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis [See PRECAUTIONS: Laboratory Tests].

Thrombotic Events:
Thrombotic events have been reported in association with IGIV (See ADVERSE REACTIONS). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [See PRECAUTIONS: Laboratory Tests].

Transfusion-Related Acute Lung Injury (TRALI):
There have been reports of non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion.
Patients with TRALI may be managed by using oxygen therapy with adequate ventilatory support. IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and patient serum [See PRECAUTIONS: Laboratory Tests].

Information For Patients:
Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.
It is recommended that the lot number of the vials used be recorded when Flebogamma® 5% DIF is administered.

Laboratory Tests:
Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed before the initial infusion of Flebogamma® 5% DIF in patients judged to have a potential increased risk for developing acute renal failure and again at appropriate intervals thereafter.

Following infusion of Flebogamma® 5% DIF, there may be a transitory rise of various antibody titers that may result in misleading positive results in serological testing.
Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and patient serum.

Pregnancy Category C:
Animal reproduction studies have not been performed with Flebogamma® 5% DIF. It is also not known whether Flebogamma® 5% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Flebogamma® 5% DIF should be given to a pregnant woman only if clearly needed.

Drug Interactions:
Antibodies in Flebogamma® 5% DIF may interfere with the response to live viral vaccines, such as measles, mumps, and rubella. Physicians should be informed of recent therapy with Immune Globulin Intravenous (Human) so that administration of live viral vaccines, if indicated, can be appropriately delayed 3 or more months from the time of IGIV administration.

Pediatric Use:
The above mentioned clinical trial with Flebogamma® 5% DIF enrolled only a very limited number of children (0) and adolescents (3) with primary humoral immune deficiency, a number insufficient to fully characterize and establish the efficacy and safety in pediatric patients.

Geriatric Use:
Subjects over 65 are at increased risk of renal failure with IGIV treatment. For these subjects, and for any other subjects at risk of renal failure, the infusion rate of Flebogamma® 5% DIF should be limited to < 0.06 mL/kg/min (3 mg/kg/min).

Adverse Reactions
Increases of creatinine and blood urea nitrogen (BUN) have been observed as soon as 1 to 2 days following infusion of IGIV. Progression to oliguria and anuria requiring dialysis has been observed, although some patients have improved spontaneously following cessation of treatment. Types of severe renal adverse reactions that have been seen following IGIV therapy include: acute renal failure, acute tubular necrosis, proximal tubular nephropathy, and osmotic nephrosis.
Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate [See DOSAGE AND ADMINISTRATION] must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Adverse reactions may occur more frequently when a high infusion rate is used, the treatment is the initial exposure to immunoglobulin, the immunoglobulin product has been changed to that of a different manufacturer, or there has been a long interval (more than 8 weeks) since the previous infusion. Slowing or stopping an infusion usually results in the prompt disappearance of symptoms.

Post-Marketing:
The following adverse reactions have been identified and reported during the post-approval use of IGIV products.

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
Integumentary	Stevens-Johnson Syndrome, epidermolysis, erythema multiformae, 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

Because post-marketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently.
Adverse events were reported in a study of 46 individuals with primary humoral immunodeficiency diseases receiving infusions every 3 to 4 weeks of 300 to 600 mg/kg body weight. Forty-three (94%) subjects experienced at least 1 adverse event irrespective of the relationship with the product, and these subjects reported a total of 595 adverse events. None of the 46 subjects who participated in this study discontinued the study prematurely due to an adverse experience related to the study drug. One subject had treatment-emergent bronchiectasis, mild, ongoing, after infusion #10; and one subject had recurrent moderate leukopenia after the 7th and 12th infusions. No adverse events occurred with an incidence of > 2% on a per infusion basis.

Table 1. Adverse Events Occurring with an Incidence of > 15%

Adverse Event	Number of AEs	Number of Subjects with AEs	Percent of Subjects with AEs
Combined Bronchitis	19	14	30
Cough and productive cough	10	10	22
Diarrhea NOS[a]	14	9	20
Headache NOS and sinus headache	46	16	35
Nasal congestion	11	7	15
Injection site reaction NOS	13	7	15
Pyrexia	27	17	37
Arthralgia	11	7	15
Sinusitis NOS	38	20	44
Pharyngitis	9	8	17
Upper respiratory tract infection	24	15	33
Wheezing and asthma aggravated	24	10	22

a. NOS = not otherwise specified
The total number of AEs (regardless of attribution) reported whose onset was within 72 hours after the end of an infusion of Flebogamma® 5% DIF was 216. There were a total of 709 infusions, resulting in a rate of 0.305 (95% confidence interval 0.225 to 0.412) temporally associated AEs per infusion. There were 144 infusions (20.1%, 1-sided 95% upper bound confidence interval = 24.4%) associated with 1 or more AEs that began within 72 hours after the completion of an infusion.

Table 2. Summary of Infusions with Mild, Moderate, and Severe Treatment-Related Adverse Events

Severity of AE	No. Infusions with AE	Adjusted %[a]	Confidence Interval[b]
Mild	58	7.9	10.4
Moderate	25	3.6	4.9
Severe	1	0.1	0.3

a. Adjusted % = average of the % of infusions with a treatment-related adverse event for each individual subject.
b. The 95% upper bound for the adjusted % of infusions for which at least 1 treatment-related adverse event was reported was derived by using the t-statistic.

The number and percent of subjects with treatment-emergent rises in AST or ALT are in Table 3.

Table 3. Number (%) of Subjects with Treatment-Emergent Rises in AST or ALT (N = 46)

Laboratory Test	Assessment Criteria	n	%
AST	Above 3x the ULN[a]	3	6.5
ALT	Above 3x the ULN	1	2.2

a. ULN = upper limit of normal.
None of these subjects had a concomitant treatment-emergent rise in total bilirubin.

Reported adverse reactions with Flebogamma® 5% DIF and other IGIV products include: 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, often beginning within 60 minutes of the start of the infusion.
Rarely, Immune Globulin Intravenous (Human) can induce a severe fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with IGIV. In the case of shock, the current standard medical treatment for shock should be implemented.

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Scientists Flying the Coop on Flu Vaccine Manufacturing

The current H1N1 pandemic exemplifies the need for more expeditious production of flu vaccine, and two companies have placed this technology just within reach.

by Ronale Tucker Rhodes, MS

IN 2005, THE world faced a possible flu pandemic known as the avian flu. Then-President George W. Bush's response was to invest $7.1 billion in preparedness funding that would give the U.S. more versatility to deal with potential biothreats, both natural and man-made. Yet, while the avian flu outbreak never produced to pandemic proportions and only $3.3 billion was invested, the money did pave the way for what looks to be a substantial improvement in vaccine production technology. That paved road has meandered somewhat, but what is finally emerging is a new recombinant flu vaccine that will outpace the current research to produce a mammalian cell-based flu vaccine and that eventually will replace the five-decades-old egg-based vaccine.

The Long and Winding Road

Traditional egg-based vaccine technology was once considered groundbreaking. And for more than 50 years, it has provided protection against influenza for 50 to 80 percent of the population. But a flu virus grown in chicken eggs has its complications. Vaccinating the entire population would potentially require 600 million eggs. If we were to experience an outbreak of avian flu, our egg-producing flocks could be depleted. Even more serious: A full-blown pandemic like the Spanish flu of 1918 would not be able to be contained and defeated by egg-based production; the process takes too long,

and eggs don't grow on demand. And, many people are allergic to eggs and can't be vaccinated.

All of the major players in the vaccine industry have long recognized the need for a more expeditious vaccine production technology, which is why in the mid-1990s, many embarked on the development of flu vaccine with mammalian-based cell cultures. In the mid-2000s, the Department of Health and Human Services (HHS) invested more than $1.5 billion in contracts with six manufacturers to develop it. Unfortunately, this technology hasn't solved the expediency issue at all because it requires the same process to produce vaccines as does egg-based technology. While it has been reported that mammalian cell-based technology could reduce the time to produce vaccines by about 10 weeks, this is only the case if the strain is ready for production. A seed stock virus, which is used in egg-based and mammalian cell-based production, takes eight weeks to be modified to reduce pathogenicity in humans. Further hindering the expediency issue is that mammalian cell-based technology yield is about fourfold lower, meaning a much larger volume is needed. This is problematic because upfront costs for operational readiness of plants are much higher than the costs for egg-based systems. Large-scale egg-based facilities have been reported to cost $150 million to produce 100 million doses per season, compared to mammalian cell-based facilities, which cost up to $600 million to produce 50 million doses per season.

Along comes the solution: Insect cell-based production. This recombinant vaccine technology cuts 10 to 12 weeks off of the production time, and has the potential of a much higher yield, specifically a greater than 40-fold productivity in terms of doses of vaccine per liter of cell culture. Even more significant is the fact that the process provides an exact match to the wild-type influenza strain, meaning it is much more effective in preventing the flu. And, the vaccine is considerably cheaper to produce.

Leaders in Cell-Based Technology

A couple of the current leaders in recombinant vaccine production tech-

sanofi pasteur

The vaccines division of sanofi-aventis Group

The need for **pertussis protection** runs in the family

Tdap[a] is the standard of care for helping protect adults and adolescents from pertussis.

- The ACIP[b] recommendations are clear—ALL eligible adults and adolescents 11-64 years of age should receive a single Tdap booster[1,2]
- Adacel vaccine is the original tetanus, diphtheria, and acellular pertussis booster vaccine for people 11 through 64 years of age[3]
- Over 35 million doses supplied since licensure in 2005[4]

CPT®[c] Code: 90715

Have you recommended Adacel vaccine today?

Indication

Adacel vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria, and pertussis as a single dose in persons 11 through 64 years of age.

Safety Information

The most common local and systemic adverse reactions to Adacel vaccine include injection site pain, erythema, and swelling; headache, body ache, tiredness, and fever. Other adverse reactions may occur. Adacel vaccine is contraindicated in persons with known systemic hypersensitivity to any component of the vaccine or a life-threatening reaction after previous administration of the vaccine or a vaccine containing the same substances. Because of uncertainty as to which component of the vaccine may be responsible, no further vaccination with the diphtheria, tetanus, or pertussis components found in Adacel vaccine should be carried out. The decision to give Adacel vaccine should be based on the potential benefits and risks; if Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid; if progressive or unstable neurologic disorders exist; or if adverse events have occurred in temporal relation to receipt of pertussis-containing vaccine. Encephalopathy within 7 days of administration of a previous dose of a pertussis-containing vaccine is a contraindication. Vaccination with Adacel vaccine may not protect all individuals.

Before administering Adacel vaccine, please see brief summary of full Prescribing Information on next page.

To order Adacel vaccine, log onto **VaccineShoppe.com**® or call **1-800-VACCINE** (1-800-822-2463).

Learn more about pertussis disease and prevention at **www.ADACELVACCINE.com**.

Adacel vaccine is manufactured by Sanofi Pasteur Limited and distributed by Sanofi Pasteur Inc.

References: 1. Centers for Disease Control and Prevention (CDC). Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR*. 2006;55(RR-17):1-37. **2.** CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2006;55(RR-3):1-43. **3.** Adacel vaccine [Prescribing Information]. Swiftwater, PA. Sanofi Pasteur Inc.; 2008. **4.** Sanofi Pasteur Inc. Data on file (Adacel direct and indirect doses, 2005-2009 US, Sanofi Pasteur and VaxServe), February 2009. MKT17191.

Adacel®

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

Arming More People Against Pertussis

[a] Tdap = Tetanus, diphtheria, and acellular pertussis. [b] ACIP = Advisory Committee on Immunization Practices.
[c] CPT = Current Procedural Terminology is a registered trademark of the American Medical Association.

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Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

℞ only

Adacel®

Brief Summary: Please see package insert for full prescribing information.

INDICATIONS AND USAGE Adacel vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis as a single dose in persons 11 through 64 years of age. The use of Adacel vaccine as a primary series, or to complete the primary series, has not been studied. Vaccination with Adacel vaccine may not protect all of vaccinated individuals.

CONTRAINDICATIONS A severe allergic reaction (e.g., anaphylaxis) after a previous dose of Adacel vaccine or any other tetanus toxoid, diphtheria toxoid or pertussis containing vaccine or any other component of this vaccine is a contraindication to vaccination with Adacel vaccine. Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered. (1,2) Encephalopathy within 7 days of a previous dose of a pertussis containing vaccine not attributable to another identifiable cause is a contraindication to vaccination with Adacel vaccine. (1-3)

WARNINGS Persons who experienced Arthus-type hypersensitivity reactions (e.g., severe local reactions associated with systemic symptoms) (4) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given emergency doses of tetanus toxoid containing vaccines more frequently than every 10 years, even if the wound is neither clean nor minor. (1,2,5,6) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give Adacel vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.(1-3) In the following situations, Adacel vaccine should generally be deferred:

- Moderate or severe acute illness with or without fever, until the acute illness resolves. (1,2)
- In adolescents, progressive neurologic disorder, including progressive encephalopathy, or uncontrolled epilepsy, until the condition has stabilized. (2)
- In adults, unstable neurologic condition (e.g., cerebrovascular events and acute encephalopathic conditions), until the condition has resolved or is stabilized. (1)

PRECAUTIONS General Before administration of Adacel vaccine, the patient's current health status and medical history should be reviewed in order to determine whether any contraindications exist and to assess the benefits and risks of vaccination. (See **CONTRAINDICATIONS** and **WARNINGS.**) Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents and equipment should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. If Adacel vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.

Information for Vaccine Recipients and/or Parent or Guardian Before administration of Adacel vaccine, health-care providers should inform the vaccine recipient and/or parent or guardian of the benefits and risks. The health-care provider should inform the vaccine recipient and/or parent or guardian about the potential for adverse reactions that have been temporally associated with Adacel vaccine or other vaccines containing similar components. The health-care provider should provide the Vaccine Information Statements (VISs) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The vaccine recipient and/or parent or guardian should be instructed to report any serious adverse reactions to their health-care provider. Females of child-bearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy surveillance system to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Adacel vaccine during pregnancy. If they are pregnant or become aware they were pregnant at the time of Adacel vaccine immunization, they are encouraged to contact directly or have their health-care professional contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). Reporting adverse events after vaccination to VAERS (Vaccine Adverse Event Reporting System) by recipients and/or parents or guardian should be encouraged. The toll-free number for VAERS forms and information is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Drug Interactions Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. (See **PRECAUTIONS, General.**) For information regarding simultaneous administration with other vaccines refer to the **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections.

Carcinogenesis, Mutagenesis, Impairment of Fertility No studies have been performed with Adacel vaccine to evaluate carcinogenicity, mutagenic potential, or impairment of fertility.

Pregnancy Category C Animal reproduction studies have not been conducted with Adacel vaccine. It is also not known whether Adacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adacel vaccine should be given to a pregnant woman only if clearly needed. Animal fertility studies have not been conducted with Adacel vaccine. The effect of Adacel vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered Adacel vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of Adacel vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study. (7)

Nursing Mothers It is not known whether Adacel vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Adacel vaccine is given to a nursing woman.

Pediatric Use Adacel vaccine is not indicated for individuals less than 11 years of age. (See **INDICATIONS AND USAGE.**) For immunization of persons 6 weeks through 6 years of age against diphtheria, tetanus and pertussis refer to manufacturers' package inserts for DTaP vaccines.

Geriatric Use Adacel vaccine is not indicated for individuals 65 years of age and older. No data are available regarding the safety and effectiveness of Adacel vaccine in individuals 65 years of age and older as clinical studies of Adacel vaccine did not include participants in the geriatric population.

ADVERSE REACTIONS The safety of Adacel vaccine was evaluated in 4 clinical studies. A total of 5,841 individuals 11-64 years of age inclusive (3,393 adolescents 11-17 years of age and 2,448 adults 18-64 years) received a single dose of Adacel vaccine. The principal safety study was a randomized, observer-blind, active controlled trial that enrolled participants 11-17 years of age (Adacel vaccine N = 1,184; Td vaccine N = 792) and 18-64 years of age (Adacel vaccine N = 1,752; Td vaccine N = 573). Study participants had not received tetanus or diphtheria containing vaccines within the previous 5 years. Solicited local and systemic reactions and unsolicited adverse events were monitored daily for 14 days post-vaccination using a diary card. From days 14-28 post-vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician's office or hospitalization, was obtained via telephone interview or at an interim clinic visit. From days 28 to 6 months post-vaccination, participants were monitored for unexpected visits to a physician's office or to an emergency room, onset of serious illness and hospitalizations. Information regarding adverse events that occurred in the 6 month post-vaccination time period was obtained from the participant via telephone. Approximately 96% of participants completed the 6-month follow-up evaluation. In the concomitant vaccination study with Adacel and Hepatitis B vaccines, local and systemic adverse events were monitored daily for 14 days post-vaccination using a diary card. Local adverse events were only monitored at site/arm of Adacel vaccine administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, i.e., up to six months post-vaccination. In the concomitant vaccination study with Adacel vaccine and trivalent inactivated influenza vaccine, local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, i.e., up to 84 days, only events that elicited seeking medical attention were collected. In all the studies, participants were monitored for serious adverse events throughout the duration of the study. Because clinical trials are conducted under widely varying conditions, 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 the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

Serious Adverse Events in All Safety Studies Throughout the 6-month follow-up period in the principal safety study, serious adverse events were reported in 1.5% of Adacel vaccine recipients and 1.4% in Td vaccine recipients. Two serious adverse events in adults were neuropathic events that occurred within 28 days of Adacel vaccine administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials and there were no additional neuropathic events reported.

Solicited Adverse Events in the Principal Safety Study Most selected solicited adverse events (erythema, swelling, pain and fever) that occurred during Days 0-14 following one dose of Adacel vaccine or Td vaccine were reported at a similar frequency. Few participants (<1%) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 63 to 78% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of Adacel vaccine compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the Adacel vaccine and Td vaccine groups. Among adults the rates of pain, after receipt of Adacel vaccine or Td vaccine, did not significantly differ. Fever of 38°C and higher was uncommon, although in the adolescent age group, it occurred significantly more frequently in Adacel vaccine recipients than Td vaccine recipients. (7) Among other solicited adverse events headache was the most frequent systemic reaction and was usually of mild to moderate intensity. In general, the rates of the events following Adacel vaccine were comparable with those observed with Td vaccine. Local and systemic solicited reactions occurred at similar rates in Adacel vaccine and Td vaccine recipients in the 3 day post-vaccination period. Most local reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). The rates of unsolicited adverse events reported from days 14-28 post-vaccination were comparable between the two groups, as were the rates of unsolicited adverse events from day 28 through 6 months. There were no spontaneous reports of whole-arm swelling of the injected limb in this study, nor in the other three studies which contributed to the safety database for Adacel vaccine.

Adverse Events in the Concomitant Vaccine Studies

Local and Systemic Reactions when Given with Hepatitis B Vaccine The rates reported for fever and injection site pain (at the Adacel vaccine administration site) were similar when Adacel and Hep B vaccines were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the Adacel vaccine administration site were increased when co-administered. Swollen and/or sore joints were reported by 22.5% for concomitant vaccination and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups. (7)

Local and Systemic Reactions when Given with Trivalent Inactivated Influenza Vaccine The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of Adacel vaccine and TIV. However, pain at the Adacel vaccine injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events were similar between the 2 study groups. (7)

Additional Studies An additional 1,806 adolescents received Adacel vaccine as part of the lot consistency study used to support Adacel vaccine licensure. This study was a randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of Adacel vaccine when given as a booster dose to adolescents 11-17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post-vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all participants. Headache was the most frequently reported systemic event occurring in approximately 44% of all participants. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days. (7) An additional 962 adolescents and adults received Adacel vaccine in three supportive Canadian studies used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following Adacel vaccine were similar to those reported in the four principal trials in the US with the exception of a higher rate (86%) of adults experiencing 'any' local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in four principal trials conducted in the US. (7) There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous reports among the 962 Adacel vaccine recipients in the supportive Canadian studies.

Postmarketing Reports The following adverse events have been spontaneously reported during the post-marketing use of Adacel vaccine in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting or the strength of causal association to Adacel vaccine. *General disorders and administration site conditions:* Large injection site reactions (>50 mm), extensive limb swelling from the injection site beyond one or both joints, Injection site bruising, sterile abscess. *Nervous system disorders:* Paraesthesia, hypoesthesia, Guillain-Barré syndrome, facial palsy, convulsion, syncope, myelitis. *Immune system disorders:* Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension) *Skin and subcutaneous tissue disorders:* Pruritus, urticaria. *Musculoskeletal and connective tissue disorders:* Myositis, muscle spasm. *Cardiac disorders:* Myocarditis

Additional Adverse Events Additional adverse events, included in this section, have been reported in conjunction with receipt of vaccines containing diphtheria, tetanus toxoids and/or pertussis antigens. Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. Such reactions may be associated with high levels of circulating antitoxin in persons who have had overly frequent injections of tetanus toxoid. (8) (See **WARNINGS.**) Persistent nodules at the site of injection have been reported following the use of adsorbed products. (4) Certain neurological conditions have been reported in temporal association with some tetanus toxoid containing vaccines or tetanus and diphtheria toxoid containing vaccines. A review by the Institute of Medicine (IOM) concluded that the evidence favors acceptance of a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. Other neurological conditions that have been reported include: demyelinating diseases of the central nervous system, peripheral mononeuropathies, and cranial mononeuropathies. The IOM has concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccines containing tetanus and/or diphtheria toxoids.

Reporting of Adverse Events The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act further requires the health-care professional to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the Vaccine Injury Table. These include anaphylaxis or anaphylactic shock within 7 days; brachial neuritis within 28 days; an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this Adacel vaccine package insert. (9-11) The US Department of Health and Human Services has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting of all adverse events occurring after vaccine administration is encouraged from vaccine recipients, parents/guardians and the health-care provider. Adverse events following immunization should be reported to VAERS. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967 or visit the VAERS website at www.vaers.hhs.gov. (9-11) Health-care providers should also report these events to Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-VACCINE).

DOSAGE AND ADMINISTRATION Adacel vaccine should be administered as a single injection of one dose (0.5 mL) by the intramuscular route. Adacel vaccine should not be combined through reconstitution or mixed with any other vaccine. Just before use, shake the vial well until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, the vaccine should not be administered. When administering a dose from a rubber-stoppered vial, do not remove either the stopper or the metal seal holding it in place. The preferred site is into the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there is a major nerve trunk. Do NOT administer this product intravenously or subcutaneously. Five years should have elapsed since the recipient's last dose of tetanus toxoid, diphtheria toxoid and/or pertussis containing vaccine. There are no data to support repeat administration of Adacel vaccine. The use of Adacel vaccine as a primary series or to complete the primary series for tetanus, diphtheria, or pertussis has not been studied.

STORAGE Store at 2° to 8°C (35° to 46°F). **DO NOT FREEZE.** Product which has been exposed to freezing should not be used. Do not use after expiration date.

REFERENCES 1. CDC. Preventing tetanus, diphtheria and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. MMWR 2006;55(RR-17):1-36. **2.** CDC. Preventing tetanus, diphtheria and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. MMWR 2006;55(RR-3):1-35. **3.** CDC. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(RR-15):1-48. **4.** CDC. Update: vaccine side effects, adverse reactions, contraindications and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45(RR-12):1-35. **5.** CDC. Diphtheria, tetanus and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(RR-10):1-28. **6.** CDC. Update on adult immunization. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(RR-12):1-52. **7.** Data on file at Sanofi Pasteur Limited. **8.** Stratton KR, et al, editors. Adverse events associated with childhood vaccines; evidence bearing on causality. Washington: National Academy Press; 1994. p. 67-117. **9.** CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(41):730-3. **10.** CDC. Current trends - national vaccine injury act: requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 1988;37(13):197-200. **11.** FDA. New reporting requirements for vaccine adverse events. FDA Drug Bull 1988;18(2):16-8.

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nology are Protein Sciences and Novavax. In June 2009, Protein Sciences Corp. was awarded a $35 million contract by the HHS when it was determined that the company was furthest along in developing a cell-based flu vaccine using its insect cell technology. And, if testing goes well, the HHS contract could be expanded over five years for a total of nearly $150 million.

The production of a recombinant flu vaccine, which Protein Sciences developed with the published genetic code of the flu virus that the CDC posts on its website, has not been without its challenges. According to CEO Dan Adams, the vaccine has been "about 12 years in the making." Challenges have included trying to partner with a large pharma company (a deal that fell through), getting clinical studies in its initial stages funded by the National Institutes of Health, getting through larger Phase III trials, and convincing the FDA that insect cells are a safe and effective way to produce vaccines.

Protein Sciences turned out its first batch of doses (about 100,000) against the H1N1 flu last June, and they're continuing to manufacture it. According to Adams, the FDA gave the company an approval date of January 2010. Adams predicts that in 2010, the company will produce a few million doses of flu vaccine. "If it's the H1N1 vaccine, we could produce a lot more than that," he explains. "We can make up to nine times as much pandemic vaccine." In 2011, Adams says that the company will have large-scale plants in place and they'll be able to produce as much flu vaccine as needed.

Protein Sciences isn't alone. Novavax also has been developing an insect cell-based flu vaccine. According to Jim Robinson, vice president of technical and quality operations, their vaccine "is 20 times more productive than egg-based manufacturing processes. We plan on manufacturing in reactors that are 1,000 to 2,000 liters in volume." Currently, Novavax is in Phase II studies, and they have a year or two of Phase III preparation and testing before licensing the product, Robinson says.

Both Robinson and Adams agree that the biggest challenge to producing recombinant flu vaccine is the manufacturing. "We're still struggling with that a little bit," says Adams, "but we are making a lot of progress." Novavax has built a pilot/product launch facility for $5 million that will produce up to 30 million doses of pandemic vaccine in six months and has completed conceptual design for a facility capable of making 75 million doses in six months, which would have an estimated cost of $40 million (versus 50 million doses for $600 million for mammalian cell-based production). The pilot plant will allow several million doses of vaccine to go out into the U.S. market after licensure while building a high-capacity plant, which Robinson says will take about two years to build and validate.

A couple of the current leaders in recombinant vaccine production technology are Protein Sciences and Novavax.

As of this writing, there is still not an approved vaccine that is produced in insect cells in the U.S.; however, one product is licensed in Europe. But with FDA approval of Protein Sciences' vaccine and GlaxoSmithKline's Cervarix vaccine for HPV, Robinson says Novavax should have the third such product under FDA review.

Better Late Than Never?

When the H1N1 flu threat hit, some say that the delay in producing a recombinant flu vaccine was a result of "faulty" government planning. But, Adams doesn't necessarily believe that. "As the military guy says, you go to war with the one you got, not the one you want to have," he says. The government "had to figure out how they were going to potentially meet an emergency. I can't attack their logic." But, he adds, right now, the country doesn't have the "technology to churn out 600 million doses [of flu vaccine]. Everybody knows [egg-based production] is not a short- or long-term solution. If this had been a real pandemic virus, we'd be out of luck."

The government's logic may not have been that far off. All cell-based flu vaccines will progressively capture an increasing market share in the future, says Robinson, who believes that "if you follow traditional thinking, mammalian-cell culture will replace eggs, but it will replace it slowly as capacity is available" — it may take 10 to 15 years to replace all the egg-based capacity. In the meantime, "recombinant flu vaccine has the potential to leapfrog mammalian cell technology as we can create capacity more quickly and for less capital." ❖

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

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Thriving with Hemophilia

Andy Matthews and David Ohlson face the challenges of severe hemophilia head on. As a result, they've learned to thrive, not just survive, with a debilitating disease. Their mission? To help others do the same.

By TRUDIE MITSCHANG

Andy Matthews has been actively involved in the hemophilia community for more than 18 years.

ANDY MATTHEWS AND David Ohlson are both married with young children. They share a passion for giving back and speaking out for causes they believe in. And they are considered a rarity within the medical community: They are active, athletic men in their early 40s living with severe hemophilia.

Diagnosed as infants, Andy, 43, and David, 44, have a unique perspective when it comes to cataloging the evolution of care for this rare bleeding disorder. Three decades ago, hemophilia homecare was nonexistent and life expectancy for many patients did not exceed adolescence, even before the HIV/AIDS transfusion catastrophe of the 1980s. Thanks to medical breakthroughs and prophylactic care, prospects for today's hemophilia patients are much better. But Andy and David recall a time when routine events like family vacations had the potential to turn into life-threatening situations. Andy remembers needing to travel with cryoprecipitate (a concentrated form of plasma) stored in dry ice, just in case he needed a transfusion on the road. At hotels, and later at college, Andy's plasma had to be stored in a restaurant deep freezer. David's experiences growing up were no less challenging.

"When I was 8, we were preparing for a Disneyland vacation. While jumping on my bed in excitement, I smacked my knee on the headboard," he says. "I didn't tell my parents right away, but two hours into the trip it was obvious I was in real trouble."

Instead of spending a week at Disneyland, David spent the week in a Los Angeles hospital. "The final two days of our trip, we went to Disneyland with me in a wheelchair. The good news was we got bumped to the front of each line, so there's always a bright side!" he laughs.

The ability to look on the bright side is a characteristic David and Andy share, and is at least part of the reason the two friends now oversee a website and blog reaching out to the hemophilia community. Their site, titled Sweet Affliction, offers educational content, resources and a platform for people to share their own stories, struggles and victories.

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GRIFOLS

David Ohlson has served as board president for the Utah Hemophilia Foundation for the past three years.

"Hemophilia can be a very difficult disease to manage, but it has given us a different perspective on life that we would otherwise never have experienced," Andy says. "I call this our 'sweet affliction,' because if you look at it as a blessing rather than a curse, your whole point of view changes."

Health insurance is obviously a big concern for anyone living with a chronic disease. While Andy was able to remain under a form of his mother's policy, known as a conversion policy, for many years into adulthood, he advocates that younger patients become highly educated about various insurance loopholes and care restrictions. He also encourages young patients to pursue higher education to improve their future insurance coverage options.

"The world of insurance is changing, and insurance companies are moving into the business of hemophilia management," Andy says. "It can feel like learning a foreign language. But once you know what the language means, you can handle it."

"Insurance and access to treatment are always issues," David explains. "It's important for those living with this disease to push for standards-of-care legislation and advocate for increased lifetime insurance caps."

While public advocacy is important and can provide a sense of purpose and accomplishment, David is also quick to note it's vital for anyone facing life with hemophilia to maintain a positive attitude and set personal goals. "Maybe you can't be a major league baseball player but you can excel academically or creatively. The key is to look at what you've been given and see how you can make a difference."

David has served as board president for the Utah Hemophilia Foundation for the past three years, a position he says he has been privileged to hold. Andy has been actively involved in the hemophilia community for more than 18 years, and currently speaks publicly on insurance issues and motivating young people to pursue education beyond a high school diploma. To learn more about their mission or to post a story, visit www.sweetaffliction.com. ❖

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

Hemophilia Quick Facts

- Hemophilia is an inherited disease. People with hemophilia have a deficiency of a blood protein, also called a "clotting factor," that is necessary to clot the blood and stop bleeding. The disease affects 1 in every 5,000 to 10,000 males.
- There are about 20,000 people in the United States living with hemophilia.
- Treatment for hemophilia endeavors to replace the missing factor intravenously and protocols vary depending on the severity of the condition.
- The first effective means of treating hemophilia involved infusing cryoprecipitate, a cold-insoluble solid that forms when frozen blood plasma is thawed. Cryoprecipitate was first used to treat hemophilia in 1964. Today, treatment has evolved to include prophylactic infusions of factor VIII and recombinant factor VIII.
- Eighty percent of people with severe hemophilia contracted the HIV/AIDS virus from blood-clotting products used in the 1980s. As a result, there are very few people with severe hemophilia over the age of 40 who are alive today.
- There is no cure for hemophilia, but advances in gene therapy have shown promise in clinical trials.
- The cost of care for a blood disorder has risen dramatically. New expensive methods have been developed to produce factor that is free of life-threatening viruses and blood-borne pathogens. A person with severe hemophilia can easily spend $180,000 or more for annual factor and medical care expenses. Complications such as major surgery can increase the costs dramatically.

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  - 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**.

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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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Transformational Leadership

Transformational leadership is a process in which "leaders and followers help each other to advance to a higher level of morale and motivation." — James MacGregor Burns

by TRUDIE MITSCHANG

BY ALL ACCOUNTS, Lawrence (Larry) Stern has been a transformational leader for his organization, as well as the biotherapeutics industry. After spearheading the plan that resulted in the formation of Talecris in 2005, Stern had his work cut out for him. Tasked with building a team and turning what was essentially a set of assets into a high-performing independent company, Stern was more than up for the challenge. Under his leadership, that initial acquisition — a company with 1,600 employees — is now a global workforce of more than 4,700.

"In less than five years, we brought over 3,000 employees on board, while also taking a leadership role in the industry by opening more plasma centers than anyone else," Stern says. "The process has been both challenging and rewarding."

A Differentiating Leadership Style

Today, Talecris is recognized as an independent, industry-leading global provider of plasma-derived protein therapies. The company's phenomenal growth culminated in a headline-making listing on NASDAQ; the IPO was the second largest in the U.S. last year.

Stern attributes this success in part to a self-described situational leadership style. His contention is that leaders need to have the flexibility to respond to situations differently based upon the circumstances and individuals involved. This ability to readily adapt is a skill set that has served him well.

"When it comes to effective leadership, some key attributes include a willingness to listen, discuss and debate, to stand firm, and the ability to communicate a clear sense of purpose and direction," Stern says. "It's also imperative to promote a sense of teamwork — this is something I strive to do and I believe it's a differentiator for us."

Talecris has invested heavily in research and development, releasing the only FDA-approved therapeutic indication for treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) in 2008. Their product, Gamunex, now has the broadest set of FDA-approved indications of any liquid intravenous immune globulin (IVIG) therapy. Gamunex also became the first and only IVIG therapy approved to treat a neurological disorder in the U.S.

"We are proud to be the first company to prove the efficacy of an IVIG product for the treatment of CIDP," says Stern. "The approval of Gamunex for a neurological disorder demonstrates our commitment to discovering innovative solutions for patients through our highly-skilled research and development team."

Putting Patients First

Not surprisingly, Talecris' accomplishments have garnered a fair share of accolades within the biopharmaceutical industry, and beyond. Last summer, the Genetic Alliance honored Talecris with its Art of Industry Partnership Award, which recognizes companies that have provided significant support to advocacy organizations and helped advance the understanding and treatment of genetic diseases. Stern says the award helped reinforce the motive behind his company's mission, which is driven by a passion to put patients' needs first.

"Our mission statement is in the hearts and souls of the people who work here, which is why we've been able to achieve so much in a short period of time. We are committed to helping people with chronic diseases, whether it's PIDD, CIDP, Alpha 1 or hemophilia, and our sense of urgency comes from knowing that the products we carry change people's lives."

Stern says the patients he's met over the years have given him inspiration as both a business leader and a human being. Like many who work with the chronically ill, he draws encouragement from watching people face the hardships of disease head on.

"So many of the patients we meet show such amazing strength and depth of character. Often, they go on to lead positive change within their communities," he says, adding that one of his favorite pursuits is interfacing with patients and advocacy groups within the various disease states.

Under his leadership, that initial acquisition — a company with 1,600 employees — is now a global workforce of more than 4,700.

Blazing New Trails

As he looks to the future, Stern says that resting on laurels is not an option for him or Talecris. He plans to continue blazing new trails through transformational change initiatives that include capital expansion and research and development of innovative new therapies. Recently, Talecris submitted a biologics license application to the FDA for a subcutaneous version of Gamunex. And in October of last year, the company received FDA approval for Prolastin-C, which benefits patients with AAT deficiency through reduced infusion times. Other breakthrough new products are currently in the Talecris research and development pipeline, including Plasmin, a naturally occurring thrombolytic agent.

"The fact that we can now identify a protein and use the available technology to extract it from plasma, go through the clinical trials and bring it to market, all under the Talecris regime, really shows the breadth of our capabilities," Stern says. "Products like these can take more than five years to finalize, and as a company, we're taking a long-term view when it comes to investments that will ultimately support better outcomes for the patients we serve." ❖

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

This advertisement is distributed as part of the American Lung Association's *Faces of Influenza* educational initiative. For more information, please visit www.facesofinfluenza.org.

Are *you* a Face of Influenza?

(More than 4 out of 5 people reading this are — get immunized.)

Influenza is not the common cold. It's serious. There are many "faces" of influenza.

In fact, annual influenza vaccination is recommended for more than 4 out of every 5 people.

Influenza vaccine is safe and effective and annual vaccination is the best way for people to protect themselves and their loved ones against influenza and its complications. Vaccination typically begins in October and can continue through March. In most seasons, influenza virus activity peaks in February or March, so vaccination throughout the entire influenza season is beneficial and recommended.

To learn more about the American Lung Association *Faces of Influenza* program, visit our Web site www.facesofinfluenza.org.

AMERICAN LUNG ASSOCIATION®

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American Lung Association's Influenza Prevention Program

In collaboration with sanofi pasteur

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Are You a "Face" of Influenza?

There are many "faces" of influenza — people who should be immunized against influenza every year. More likely than not, each one of us knows someone whose well-being, good health, or life depends on getting an influenza immunization each and every year. Take the quiz below to see if you are a "face" of influenza.

- ☐ Are you a close contact, such as a parent, sibling, grandparent, or babysitter, of a child younger than 6 months of age?
- ☐ Do you have a child 6 months – 18 years of age?[1]
- ☐ Will you be an expectant mother during the influenza season (September – May)?
- ☐ Are you 50 years of age or older?
- ☐ Do you have a chronic health condition, such as asthma, chronic obstructive pulmonary disease (COPD), heart disease, or diabetes?
- ☐ Do you live with someone with a chronic medical condition, such as asthma, COPD, heart disease, or diabetes?
- ☐ Do you work in a health-care profession or facility?[1,2]

If you checked one or more of these questions you could be one of the many "faces" of influenza, people who should get vaccinated against influenza each and every year. Talk to your doctor or health-care provider about influenza vaccination today.

Influenza is not the common cold. It's serious.

Annual immunization is the best way to protect against influenza. We at the American Lung Association urge you and your loved ones to get vaccinated as soon as you can. Vaccination typically begins in October and can continue through March. In most seasons, influenza virus activity doesn't peak until February or March. Influenza vaccination is a safe and effective way to help prevent influenza.[2]

FACES OF INFLUENZA™
American Lung Association's Influenza Prevention Program
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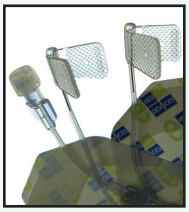
BioProducts

Glucocard 01-Mini

The Glucocard 01-mini blood glucose monitoring system contains the latest technology and delivers fast and accurate test results with a tiny sample size. Features include auto coding, seven-second test time, more than 20 free interchangeable face plates, pre/post-meal flagging, 50-count test memory, time and date stamp, seven-, 14- or 30-day averaging, plasma referenced results and a five-year warranty.
Arkray, (800) 888-5957, www.glucocardusa.com

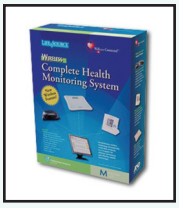


Safety SCIG Infusion Sets

The family of Safety SCIG multi-needle infusion therapy products for pediatric and adult patients features ultra-flexible polyethylene tubing; a 27-gauge needle (available in 6 mm to minimize patient trauma or 9 mm for patients with thicker skin); optimized needle contour curvature to ensure maximum flow through the needle; and a translucent wing to facilitate insertion and provide stability for long-term use. Hypoallergenic dressings are included with each needle site for ease of placement. Special accessories ensure compatibility with all major ambulatory infusion pumps. Special connectors, accessories or design adaptations are available for specific infusion pumps.
eMedical Devices, (888) 550-6500, emedicaldevices.com/scig-infusion-sets-s.html

Apidra SoloSTAR

The Apidra SoloSTAR is an easy-to-use insulin pen for adults with type 2 diabetes or adults and children (4 years and older) with type 1. It comes prefilled with Apidra, from the maker of Lantus. Doses can be set from 1 to 80 units one unit at a time. Other features include a dose window, dosage knob and injection button.
Sanofi Aventis, www.apidra.com



Wireless Health Monitoring System

The Wireless Complete Health Monitoring combo pack contains a Wireless Activity Monitor, Wireless Automatic Blood Pressure Monitor, Wireless Precision Scale, ActiLink USB Transceiver, downloadable Wellness Connected software, trilingual instruction manuals, a medium cuff and all required batteries — all designed to daily track blood pressure, weight and physical activity. The Wellness Connected software application automatically receives measurements and graphs them in a colorful, user-friendly interface. A subscription to the ActiHealth Online service allows wellness data to be viewed from any Internet-enabled computer, and progress can be tracked remotely.
A&D Medical, (888) 726-9966, www.wellnessconnected.com

Daisy Chain Needle Set

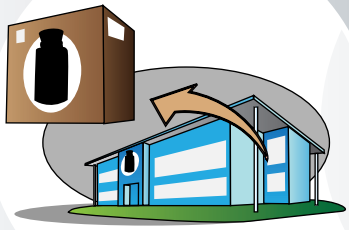
RMS Medical's new Daisy Chain Needle Set for subcutaneous infusions connects to as many sites as needed and is engineered for maximum flow. Each needle adjusts to 6 mm, 9 mm and 12 mm lengths. The set eliminates the need to sock multiple bi, tri and quad sets. Adhesive wings attach to the patient and come together after use to prevent needle stick injury.
RMS Medical, (845) 469-2042, www.rmsmedicalproducts.com/administrationsets.htm

Outlook Safety Infusion System

The Outlook Safety Infusion System helps to ensure that the right patient receives the right medication in the right dose from an authorized clinician at point-of-care. DoseScan technology allows the clinician to automate the programming of the infusion device, which reduces the primary cause of IV medication errors. And DoseGuard software technology notifies the clinician when pre-programmed dose limits are exceeded, the secondary cause of errors.
B Braun, (800) 227-2862, www.bbraunusa.com

Do you **know** where your products have been?

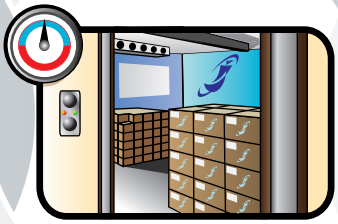
B R I N G I N G T R U S T T O



1

PURCHASING

Products are purchased only from the manufacturer – never from another distributor or source.



2

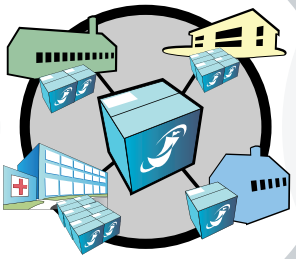
STORAGE

State-of-the-art warehouse. Checkpoints include: access, temperature and intertransit handling.

3

SPECIALTY PACKAGING

Analysis of the specific requirements of each product ensures protein integrity is maintained during storage and transit.



4

INTERACTIVE ALLOCATION

Assures responsible, demand-based distribution. Reduces potential for price gouging and gray-market purchasing to accommodate critical demand issues.

When they come from **FFF**, you can be **sure** you do.

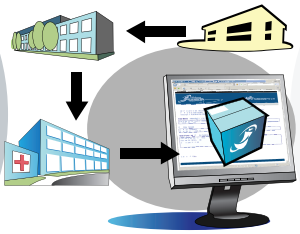
THE MARKETPLACE

5

DELIVERY
Products are delivered only to certified healthcare providers with a DEA license and only to the address on the license.

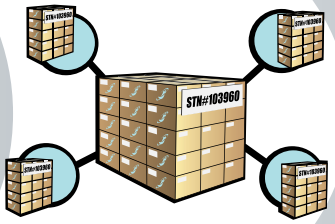
6

METHODS OF DELIVERY
Monitoring and adjusting for extreme weather conditions allow time-sensitive delivery to ensure product integrity.



7

VERIFICATION
Verified Electronic Pedigree™, FFF's proprietary system, verifies product pedigree from the manufacturer and receipt by the healthcare provider to validate our safe channel.



8

TRACKING
Lot-Track™, another FFF service, provides accurate product lot tracking and recall notification within four hours.

The 8 Critical Steps to Guaranteed Channel Integrity™

FFF Enterprises has made the uncompromising decision to purchase only from the manufacturer and sell only to licensed healthcare providers, shortening the supply chain to avoid secondary distribution channels that open the doorway to counterfeiters.

The 8 Critical Steps to Guaranteed Channel Integrity assure that patient safety, product efficacy and fair pricing are maintained throughout our safe channel. From purchasing to storage and delivery, these best practices maintain the strength of each link in the chain,
with patient welfare at the center of every decision.

(800) 843-7477 | www.FFFenterprises.com

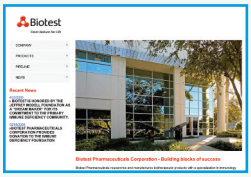
FFF enterprises
Helping Healthcare Care®

BioResources

The following websites provide useful information about plasma collection and therapies.

Baxter International Inc.

Baxter International develops, manufactures and markets products that save and sustain the lives of people with hemophilia, immune disorders, infectious diseases, kidney disease, trauma and other chronic and acute medical conditions.
www.baxter.com



Biotest Pharmaceuticals

Biotest Pharmaceuticals researches and manufactures biotherapeutic products, is a leader in the collection of source plasma and is currently involved in the development of plasma protein products in the field of primary immune deficiency.
www.biotestpharma.com

CSL Behring

CSL Behring, a global leader in the plasma protein biotherapeutics industry, researches, develops, manufactures and markets biotherapies that are used to treat serious and rare conditions. The company's website includes resources for learning about what plasma is and how it is used, why individuals should donate and how to become a donor. www.cslplasma.com

Donating Plasma

This site explains why plasma donors are needed, eligibility criteria for giving plasma and the donation process. There are also frequently asked questions about plasma donation and patient stories pages, as well as a locator for plasma collection cebters in the U.S. and abroad. www.donatingplasma.org

Grifols

Grifols, serving healthcare professionals and patients in more than 90 countries, and researches, develops, manufactures and markets plasma derivatives, IV therapy, enteral nutrition, diagnostic systems and medical materials. www.grifols.com

Immune Deficiency Foundation (IDF)

IDF is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research. The site includes information about PIs and immunoglobulin, and has an advocacy center.
www.primaryimmune.org

National Hemophilia Foundation

The National Hemophilia Foundation is dedicated to finding better treatments and cures for bleeding and clotting disorders and to preventing the complications of these disorders through education, advocacy and research. The website include information about blood and product safety and more.
www.hemophilia.org

Octapharma

Octapharma is an independent, global plasma fractionation specialist. Its core business is the development, production and sale of high-quality plasma derivatives.
www.octapharma.com

Plasma Protein Therapeutics Association (PPTA)

PPTA is an advocate for the world's leading source plasma collectors and producers of plasma-based and recombinant biological therapeutics. PPTA works with patient groups, policymakers, regulatory agencies and other stakeholders to address critical issues.
www.pptaglobal.org

Primary Immunodeficiency Resource Center

INFO4PI is the official webpage of the Jeffrey Modell Foundation and an online resource center for primary immunodeficiencies (PIs). The site is designed for all populations to be able to quickly access information on PI diseases. www.jmfworld.com

Talecris Biotherapeutics

Talecris Biotherapeutics discovers, develops and produces critical care treatments for people with life-threatening disorders in a variety of therapeutic areas. Talecris Plasma Resources is a national network of plasma collection centers that provides the source material for the production of Talecris' critical care protein therapies. www.talecris.com

BioDashboard

CALCULATOR

IVIG Reimbursement Calculator

Product	Manufacturer	HCPCS	Reimbursement Rates: Hospital Outpatient ASP+4% (per gram)	Reimbursement Rates: Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$59.808	$60.958
FLEBOGAMMA 5% DIF	Grifols	J1572	$72.847	$74.248
GAMMAGARD LIQUID	Baxter BioScience	J1569	$75.612	$77.066
GAMMAGARD S/D	Baxter	J1566	$59.808	$60.958
GAMUNEX	Talecris Biotherapeutics	J1561	$73.824	$75.244
OCTAGAM	Octapharma	J1568	$74.003	$75.426
PRIVIGEN	CSL Behring	J1459	$68.944	$70.270

Calculate your reimbursement online at www.bstquarterly.com/IVIGCalculator.aspx

Rates are effective January 1, 2010 through March 31, 2010.

REFERENCE TABLES

IG Reference Table

Product	Size	Manufacturer	Indications
CARIMUNE NF (Lyophilized)	3 g, 6 g, 12 g	CSL Behring	PIDD, ITP
FLEBOGAMMA 5% 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
GAMUNEX (Liquid, 10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Talecris Biotherapeutics	PIDD, ITP, CIDP
GAMMAPLEX (Liquid, 5%)	2.5 g, 5 g, 10 g	Bio Products Laboratory	PIDD
OCTAGAM (Liquid, 5%)	1 g, 2.5 g, 5 g, 10 g, 25 g	Octopharma	PIDD
PRIVIGEN (Liquid, 10%)	5 g, 10 g, 20 g	CSL Behring	PIDD, ITP
VIVAGLOBIN (Liquid, 16%)	3 mL, 10 mL, 20 mL	CSL Behring	PIDD

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Idiopathic thrombocytopenic purpura
KD Kawasaki disease
PIDD Primary immune deficiency disease

Injectable Influenza Vaccine

Administration Code: G0008 Diagnosis Code: V04.81

Product	Size	When Administered to Indicated Age Group	CPT Code
AFLURIA 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
FLUZONE Pediatric	0.25 mL prefilled syringe		
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		
FLUVIRIN	0.5 mL prefilled syringe		
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
FLUZONE	5 mL multi-dose vial		
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		

gamunex®

immune globulin intravenous (human), 10%
caprylate/chromatography purified

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

Talecris Biotherapeutics, Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1716

08939392/08939393-BS
Revised: October 2008

The PROOF is everywhere you look

GAMUNEX is the IGIV therapy supported by robust clinical trials

- Proven efficacy and safety in more FDA-approved indications (CIDP, PI, and ITP)* than any other liquid IGIV[1]
- The most clinically studied liquid IGIV, with >600 patients and >4100 infusions[2]

The most common drug-related adverse reactions observed at a rate ≥5% 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 observed in clinical study subjects receiving GAMUNEX 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 humoral immunodeficiency; ITP=idiopathic thrombocytopenic purpura.

References: 1. Data on file. Talecris Biotherapeutics, Inc. **2.** GAMUNEX® [package insert]. Research Triangle Park, NC: Talecris Biotherapeutics; 2008.

Important Safety Information—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). Gamunex is contraindicated in individuals with known anaphylactic or severe systemic response to Immune Globulin (Human).

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

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.

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. As with all plasma-derived therapeutics, the potential to transmit infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent that can cause disease, cannot be totally eliminated. There is also the possibility that unknown infectious agents may be present in such products.

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.

Evidence based. Patient proven.

gamunex®
immune globulin intravenous (human), 10% caprylate/chromatography purified

Talecris BIOTHERAPEUTICS

To get GAMUNEX call 1-888-MY-GAMUNEX (694-2686) USA Customer Service 1-800-243-4153 Clinical Communications 1-800-520-2807 Reimbursement *Help*line 1-877-827-3462

BioSupply Trends Quarterly
41093 County Center Drive
Temecula, CA 92591-9815

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Convenience Choose your delivery dates

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