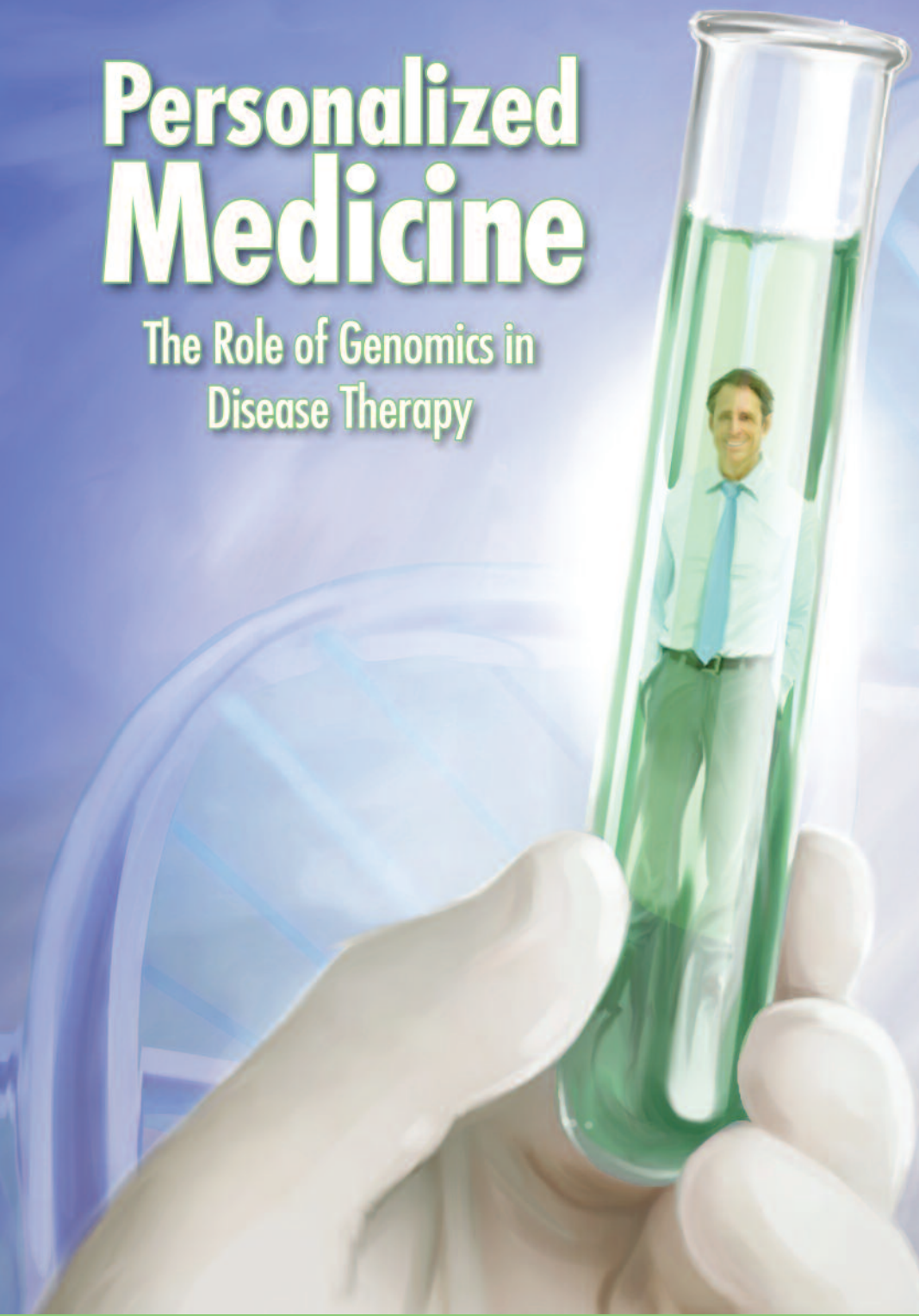
October 2010

BioSupply Trends

Special Focus: INNOVATION

Quarterly



Personalized Medicine

The Role of Genomics in Disease Therapy

High-Dose Flu Vaccine A Boost for Seniors

Healthcare Reform and Its Effects on the Industry

Misdiagnosed: A Medical Malady

Myths and Facts: Pertussis

IVIG and Alzheimer's Disease — Page 56

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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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

October 2010

Features

Special Focus: Innovation

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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Changing the World — One Idea at a Time

BILL GATES SAID, "Never before in history has innovation offered the promise of so much to so many in so short a time." How true! As we approach the end of the first decade of the new millennium, consider how many significant innovations have developed within the past 10 years alone: Social media platforms like Facebook, Twitter and Skype have become normal aspects of everyday life for both individuals and businesses. You Tube has made everyone a producer. Cell phones continue to get smarter and more interactive as our fingers do the walking — digitally. In healthcare and pharmaceuticals, major innovations have taken place in the field of regenerative medicine, now being used to heal broken bones, burns and age-related illness, among other things. Robotic-assisted surgery is routinely employed to treat everything from infertility to prostate cancer. And in the area of vaccines, studies and trials suggest that vaccines for incurable diseases like HIV and breast cancer may soon become a reality.

The bottom line: Innovation has the power to change lives. This is why it remains one of my favorite topics. In this issue of *BioSupply Trends Quarterly*, we celebrate innovation in its many facets and forms. The new high-dose flu vaccine, for example, is an innovation that addresses an obvious need: protecting those 65 years of age and older from the deadly influenza virus. According to the Centers for Disease Control and Prevention, people 65 and older account for about 90 percent of the deaths from flu-related causes each year. This new high-dose flu vaccine, then, has the potential to solve a long-standing problem by altering that trend and saving lives.

It would be difficult to discuss innovation in medicine without considering the impact of the Human Genome Project. Our cover feature, Personalized Medicine, looks at such innovative research as pharmacogenomics, a relatively new area of genetic study that focuses on tailoring drugs to an individual's genetic makeup, utilizing gene therapy to diagnose and predict disease. Without doubt, this remarkably innovative field is poised to change the way medicine is developed and dispensed and how many diseases are treated.

Healthcare reform remains a topic on the forefront of everyone's mind as we strive to improve a system that has been broken for a long time. Solutions are certainly not easy, nor easily agreed upon. This issue, in our Leadership Corner, Mike Alkire, president of Premier Purchasing Partners Inc., offers insights into the potential benefits of the new Accountable Care Organizations (ACOs) that promise to reduce healthcare costs while simultaneously improving quality of care.

Another area of healthcare that begs a closer look is the topic of medical misdiagnosis. How can we innovate to better help practitioners? With all of the diagnostic tools available to modern medicine, misdiagnosis should be a rare occurrence, but, unfortunately, as we discuss in our article, it is not. The statistics give us a wake-up call that there is clearly a need for improvement. Our hope in highlighting this challenge is that innovation can play a role in improving systems and safeguards that protect patients from preventable errors.

It is an exciting time that we live in. Sometimes the pace is so fast that human error is unavoidable and communication is so rapid that misunderstandings occur. Yet miraculous, life-saving and life-preserving advancements are occurring at such a speed that we cannot help but be astounded. Now more than ever before, the question should not be "Why?" but rather "Why not?"

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*. ❖

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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Medicare Legislative Update

Many advocates for Medicare beneficiaries are backing a new bipartisan bill to further expand off-label Part D drug coverage by modifying the rules in the prescription drug program to mirror those used in Part B. The bill would modify the Part D rules to allow plan sponsors to pay for drugs used off label to treat diseases other than cancer — such as Alzheimer's, multiple sclerosis (MS) and muscular dystrophy — if they are not in Medicare-approved compendia, but are supported by peer-reviewed literature.

The Medicare Modernization Act, which created the Part D program, originally prohibited plan sponsors from covering drugs prescribed off label unless they are listed on Medicare-approved compendia. Under Part B, which covers drugs that are administered in a doctor's office, off-label drugs are covered if their use is supported in peer-reviewed literature. The Medicare Improvement for Patients and Providers Act (MIPPA), passed in 2008, expanded Part D coverage for off-label prescriptions of cancer drugs if they were supported by peer-reviewed literature.

The new bill would use the existing Part D coverage and appeals rules to allow plan sponsors to pay for off-label drug uses on a case-by-case basis, but wouldn't mandate that coverage. Also, it would include a thorough review of the "safety and efficacy of the drugs," which have been a concern for lawmakers.

One issue the bill does not address, however, are therapies that are covered under Medicare Part D and used on an off-label basis, yet under Medicare Part B are subject to Local Coverage Determinations, which affect coverage and dosing, even if the medical literature supports their use. Another issue not addressed is the development of Tier 4 plans that allow co-insurance charges for specialty therapies under Medicare Part D. Co-insurance charges that average 20 percent to 35 percent for therapies such as IVIG can cost hundreds to thousands of dollars per month.

The bill is sponsored by first-term Ohio Democrat Mary Jo Kilroy, who suffers from MS, and is co-sponsored by two Texas Republicans: Reps. William "Mac" Thornberry and Michael Burgess. ❖

Neurologists Not Eligible for Medicare Payment Incentives and Increased Medicaid Rates

An error has led to the omission of neurologists from the list of specialists eligible to receive the Medicare payment incentives under the Patient Protection and Affordable Care Act, HR 3590, as well as increased Medicaid rates in the Health Care and Education Affordability Reconciliation Act, HR 4872.

HR 3590 provides a bonus to physicians who: 1) specialize in family medicine, internal medicine and geriatric medicine, and 2) have allowed charges for evaluation and management services that account for at least 60 percent of the physician's or practitioner's total allowed charges. HR 4872 requires that Medicaid payment rates to primary care physicians (family medicine, general internal medicine or pediatric medicine) for furnishing primary care services in 2013 and 2014 be at least 100 percent of Medicare payment rates under both fee-for-service plans and managed-care plans.

Neurology practices are heavily focused on patient evaluation, management and coordination of care, and, on average, neurologists bill 61 percent of their services as described in the second criteria of HR 3590. Efforts are under way to add neurology to the list of specialties eligible for these incentives before access to care for patients is compromised. ❖

Louisiana Passes Bill to Bypass Step Therapy

On July 2, 2010, the governor of the state of Louisiana signed into law legislation that would put the right to prescribe the best therapy for patients in the hands of physicians. In an effort to save money, insurance companies have previously required patients to first undergo step therapy, which has caused, in many cases, irreparable harm.

As of Jan. 1, 2011, Louisiana state health plans must provide coverage for step therapy or fail-first protocols. When medications for a treatment of any medical condition are restricted for use by an insurer by a step therapy or fail-first protocol, the prescribing physician shall have access to a clear and convenient process to expeditiously request an override of that restriction. An override must be considered by the insurer under any of the following circumstances: The prescribing physician can demonstrate, based on sound clinical evidence, that the preferred treatment required under step therapy or fail-first protocol has been ineffective in the treatment of the insured's disease or medical condition; is expected to be ineffective based on the known relevant physical or mental characteristics of the insured and known characteristics of the drug regimen; or will cause or will likely cause an adverse reaction or other physical harm to the insured. ❖

New York Law Prohibits Drug Specialty Tiers

The state of New York has passed a new law that prohibits commercial health insurance plans from creating specialty tiers within their prescription drug formularies. According to the law, the justification for the ban on specialty tiers is as follows:

As the cost of prescription drugs continues to climb, health insurance plans in California, Minnesota, Maryland and Alabama have created new specialty tiers to increase the co-payments that consumers pay. Instead of a three-tiered drug formulary structure used by most plans (where Tier 1 is for generics, Tier 2 is for brand-name preferred drugs, and Tier 3 is for brand-name non-preferred drugs), some plans have begun to add fourth and fifth tiers for the most expensive medications. These additional tiers assign a percentage of the cost of the medication as co-insurance, as opposed to a set dollar amount used in the other three tiers. An example might be $10 for Tier 1 generics, $25 for Tier 2 brand-name preferred drugs, and $50 for Tier 3 brand-name non-preferred drugs.

In the states allowing specialty tiers, medications placed in Tiers 4 and 5 are typically assigned a co-insurance payment of between 20 percent and 35 percent. Therefore, a patient being treated for multiple sclerosis (MS), for example, could have a monthly co-payment that could reach $775. People living with chronic illnesses, such as MS, rheumatoid arthritis and hemophilia, or people with a life-threatening condition, such as HIV, breast or colorectal cancers, leukemia and non-Hodgkin's lymphoma, are the patients who are most affected.

According to the New York law, specialty tiering is contrary to the original purpose of insurance, which is to spread the cost. Instead, it creates a structure where those who are most sick pay more, which is an unlawful discriminatory practice. ❖

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

For the treatment of hemophilia A

Take a closer look at Koāte-DVI

Proven efficacy

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

Commitment to safety

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

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

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

Experience

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

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

Important Safety Information

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

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

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

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

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

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

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

Talecris BIOTHERAPEUTICS

Printed in USA November 2009 KD44-1109

Koāte®-DVI

Antihemophilic Factor (Human)

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

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

DESCRIPTION

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

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

PRECAUTIONS

General

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

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

Pregnancy Category C

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

Pediatric Use

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

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

Information for Patient

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

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

ADVERSE REACTIONS

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

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

CAUTION

℞ only

U.S. federal law prohibits dispensing without prescription.

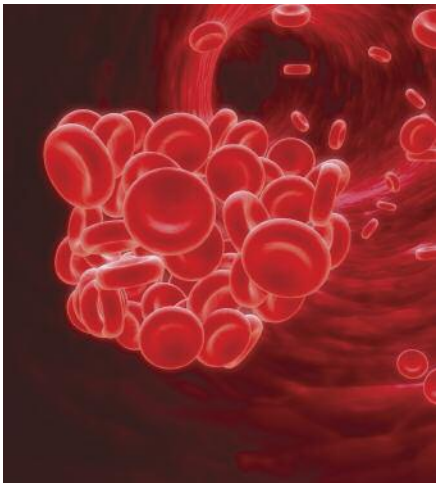
Talecris BIOTHERAPEUTICS
Talecris Biotherapeutics, Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1716

08938170-BS

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

What is the reimbursement code for the newly approved wilate, manufactured by Octapharma? How are insurance companies covering it?



In January, the U.S. Food and Drug Administration granted Octapharma orphan drug exclusivity for wilate (von Willebrand Factor/Factor VIII Concentrate, Human) for the treatment of spontaneous or trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD), as well as in patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.

From the Octapharma website (www.wilateusa.com), the reimbursement codes are as follows:

- Outpatient Prospective Payment System Payment Pass Through Code — C9267 (inj, wilate) per 100 IU VWF:RCof
- Part B Medicare HCPCS Code — J3590 (miscellaneous biologic) per 1 IU VWF:RCof

According to one large insurer, medical necessity for Factor VIII for the treatment of von Willebrand disease is considered medically appropriate if all of the following criteria are met:

1) When the disease is categorized as any one of the following: Type I (partial quantitative deficiency of von Willebrand factor) where the use of desmopressin is known/suspected to be inadequate; Type 2 (including subsets A, B, M or N with qualitative defects of von Willebrand factor); or Type 3 (complete deficiency of von Willebrand factor);

2) When the request is specifically approved for the treatment of bleeding episodes in adult and pediatric individuals with von Willebrand disease (e.g., wilate).

A major patient concern, which was found in one insurer's drug formulary, is that wilate, along with several other antihemophilic factor products, is listed in a Tier 5 level. At this level, the patient is responsible for a 33 percent copayment. While patient liability can be limited by an out-of-pocket maximum, physicians ordering wilate or any other specialty drug should be aware of the costs patients could face. To assist in reimbursement matters, Octapharma has experts available specifically for wilate. They can be reached by emailing usreimbursement@octapharma.com, calling (800) 554-4440 or faxing (800) 554-6744.

Is Medicare going to cover Fluzone High-Dose?

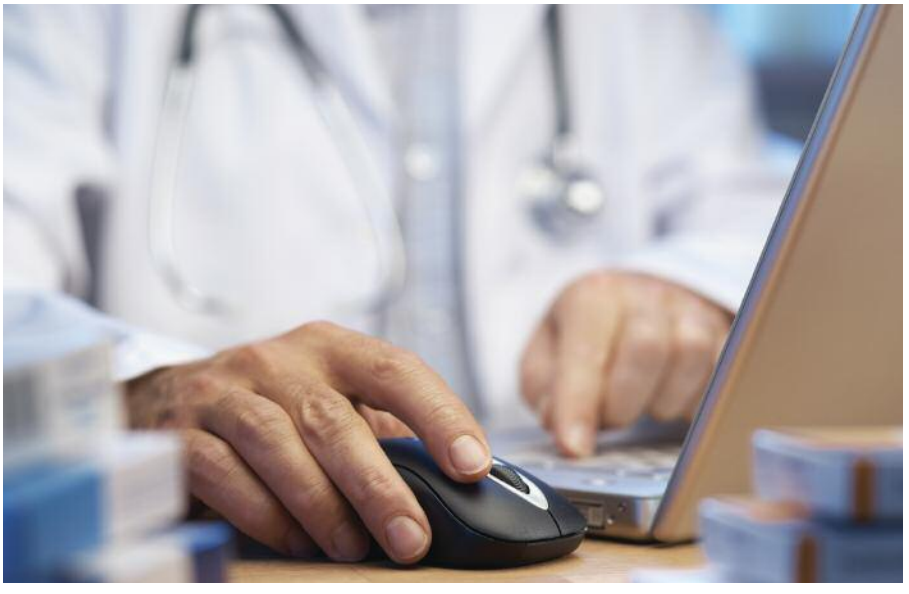
Fluzone High-Dose, an inactivated influenza vaccine containing an increased amount of antigen compared with standard-dose influenza vaccines, is available for the first time and approved by the Food and Drug Administration for adults age 65 and older who have a reduced antibody response to influenza vaccination compared with younger adults. Although the Advisory Committee on Immunization Practices (ACIP) recommends a yearly influenza vaccine for all persons over the age of 6 months, it does not currently specify a particular vaccine over another.

Medicare pays for one seasonal influenza immunization each influenza season for all beneficiaries. No coinsurance or copayment applies to this benefit, and an individual does not have to meet his or her deductible to receive the benefit. In addition, Medicare pays separate rates for the administration and cost of the influenza vaccine.

Medicare Part B will reimburse for Fluzone High-Dose for beneficiaries 65 and older using a CPT (current procedural terminology) code of 90662. As of the date of this writing, the reimbursement rate was $29.21. The Centers for Medicare and Medicaid Services (CMS) was expected to issue new average sales price (ASP) updates on October 1, 2010. For current CMS pricing, go to www.cms.gov/McrPartBDrugAvgSalesPrice/01a19_2010aspfiles.asp#TopOfPage.

Sources:
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5916a2.htm?s_cid=mm5916a2_e
http://www.cms.gov/adultimmunizations/02_providerresources.asp

Some insurance companies will cover off-label uses for Rituxan, while others will not. In what situations will Medicare cover Rituxan?



Rituxan is a monoclonal antibody that targets a specific protein, known as CD20, on the surface of B cells. Rituxan binds to CD20 and is believed to work with the body's own immune system to attack and kill the marked B cells. Food and Drug Administration (FDA)-approved indications for the uses of Rituxan include chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA) and non-Hodgkin's lymphoma (NHL).

In general, private insurers will cover at least what Medicare will cover. According to the Centers for Medicare and Medicaid Services, Medicare coverage for Rituxan is considered medically necessary for the following FDA-approved indications.

Non-Hodgkin's lymphoma (NHL):

• Patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, NHL as a single agent

• Previously untreated diffuse large B-cell, CD20-positive, NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens

• Previously untreated follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy

• Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent after first-line treatment with CVP (cyclophosphamide and vincristine) chemotherapy

Rheumatoid arthritis (RA):

• In combination with methotrexate to reduce signs and symptoms and to slow the progression of structural damage in adult patients with moderately-to severely-active RA who have had an inadequate response to one or more TNF antagonist therapies

Chronic lymphocytic leukemia (CLL):

• In combination with fludarabine and cyclophosphamide (Fc) for the treatment of patients with previously untreated and previously treated CD20-positive CLL

Medicare also will consider the use of Rituxan as medically reasonable and necessary for the FDA-approved uses, as well as the following off-labeled indications:

• Low-grade or follicular CD20-positive, B-cell non-Hodgkin's lymphomas (re-induction treatment appropriate for responders and patients with stable disease)

• Intermediate and high-grade NHL when used as a single agent, in combination with a CHOP chemotherapy regimen, or in combination with other agents active in the disease

• Immune or idiopathic thrombocytopenia purpura

• Evans syndrome

• Waldenstrom's macroglobulinemia

• Refractory thrombotic thrombocytopenic purpura (TTP) for patients who do not respond to plasmapheresis

• Autoimmune hemolytic anemia condition that is refractory to conventional treatment (e.g., corticosteroid treatment and splenectomy). ❖

Source: http://www.cms.gov/mcd/viewlcd.asp?lcd_id=29271&lcd_version=4&show=all

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

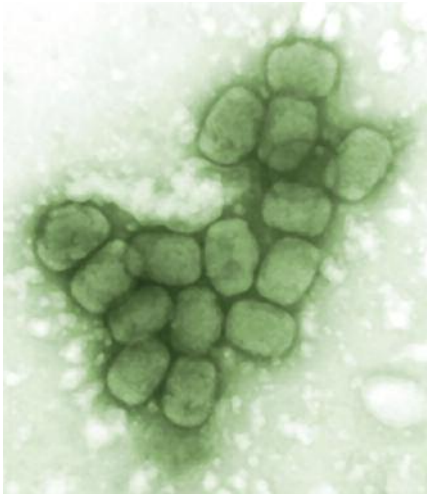
Ask Our Experts

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

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

Vaccines

New, Safer Smallpox Vaccine Stockpiled



The U.S. government has begun to stockpile a new version of the smallpox vaccine that is designed to close a gap that left millions vulnerable to a bioterror attack. Denmark-based Bavarian Nordic's Imvamune is made with modified vaccinia ankara, a safer alternative to the cowpox vaccines that have been used for generations. According to officials at Bavarian Nordic, the first shipments arrived in the U.S. Strategic National Stockpile in mid-May, which was within hours of a World Health Organization ceremony marking eradication of the disease.

While natural transmission of smallpox has ceased, the virus lives in freezers at the Centers for Disease Control and Prevention in Atlanta and, possibly, in Russia, where Soviet scientists are believed to have created tons of weaponized smallpox. The U.S. government started stockpiling the vaccine a decade ago after the breakup of the Soviet Union and the rise of global terrorism. "In June 2001, we had 12 million doses of smallpox vaccine for a population of 280 million," says Randall Larsen, CEO of the nonprofit Weapons of Mass Destruction Center. Today, he says, the national stockpile contains 300 million doses of standard smallpox vaccine. ❖

Vaccines

CDC Recommends Universal Flu Vaccination

The Centers for Disease Control and Prevention (CDC) has issued a comprehensive update on seasonal flu vaccination, which includes the new universal recommendation for everyone except infants younger than 6 months old. In 2009, the CDC's seasonal flu vaccination recommendation covered 85 percent of the population. This latest expansion, which includes all healthy, nonpregnant adults ages 18 to 49, will help to address two problems: 1) flu complications can occur, even in healthy people, and 2) many adults with underlying conditions such as diabetes and asthma don't consider themselves at increased risk.

The CDC's recommendations also include its Advisory Committee on Immunization Practices' (ACIP) recent advice that children ages 6 months through 8 years who have not received at least one dose of pandemic H1N1 vaccine should receive two doses of the trivalent vaccine for the upcoming flu season, which includes the pandemic strain. The latest recommendations also say adults age 65 and older can receive either the standard seasonal flu vaccines or the new high-dose version made by Sanofi Pasteur (see the related story about the new high-dose flu vaccine on page 28).

New strategies for pitching the new universal flu vaccine recommendations also are being tested by the CDC on focus groups, which include both the public and medical providers. The campaign is available on the Parents of Kids with Infectious Diseases (PKIDs) website at www.pkids.org. According to Richard Quartarone, a media and communication officer with the National Center for Immunization and Respiratory Diseases, research has shown that vaccine messages have the most impact when they come from sources people trust, "and healthcare providers are whom they trust the most." ❖

Did You Know?

"HIV patients are 13 to 31 times more likely than the general population to develop Hodgkin's lymphoma, twice as likely to have kidney cancer and seven times as likely to have liver cancer."

— John F. Deeken

Research

MMRV Vaccine Increases Fever and Seizure Risk

Measles-mumps-rubella-varicella (MMRV) vaccination is associated with an increased risk of fever and seizure in young children, above that already associated with measles-containing vaccines, according to a recent study. The study, which was published in the June 29 online issue of *Pediatrics*, used Vaccine Safety Datalink data from 2000 to 2008, and evaluated seizure and fever visits among children ages 12 months to 23 months after MMRV and separate MMR plus varicella vaccines. Researchers found that with all measles-containing vaccines, seizure and fever significantly clustered seven to 10 days after vaccination, but this was not the case after varicella vaccination alone. In addition, during days seven to 10 after vaccination, the seizure risk was high after MMRV vaccination compared with after MMR plus varicella vaccination, with a relative risk of 1.98. Therefore, the researchers determined that MMRV vaccination leads to one additional febrile seizure for every 2,300 doses given instead of MMR plus varicella vaccines.

A previous preliminary study found that the MMRV vaccine is linked to a twofold increased risk of febrile seizures compared with separate MMR and varicella vaccines. The current study included data on twice as many vaccine recipients. ❖

Safety

New Safety Websites Launched by FDA

The U.S. Food and Drug Administration (FDA) has launched two new websites relating to drug safety. On its Postmarketing Drug Safety Evaluations site (www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm), patients and healthcare professionals can view what the FDA has learned about the safety of new drugs or biologics, such as vaccines, 18 months after approval or after 10,000 patients have used them, whichever comes later.

The second site, the Safety Reporting Portal (www.safetyreporting.hhs.gov), was launched with the National Institutes of Health and is designed to provide greater and easier access to online reporting of safety problems related to foods, including animal feed, animal drugs and adverse events occurring on human gene transfer trials. In the future, the site will encompass other types of clinical trials and, eventually, safety problems arising from products regulated by a broad array of federal agencies. ❖

Research

Low-Dose Polio Vaccine Effective

Giving just one-fifth the usual dose of the polio vaccine may protect babies against the virus nearly as well as a full dose, as long as it is injected just beneath the skin, according to a recent study. The study tested a needle-free jet injector made by Bioject Medical Technologies to deliver the vaccine beneath the skin in 373 children at ages 2 months, 4 months and 6 months. Blood tests showed that more than 95 percent of the infants mounted an effective immune response against polio. And, while babies who got a lower dose had fewer antibodies against polio, researchers said that shouldn't be a problem.

The findings could reduce the cost of immunization, an important consideration in developing countries, some of which have had trouble containing the paralytic disease. The injectable vaccine costs about $3 per dose, whereas the oral polio vaccine is much cheaper, at about 15 cents, but it contains a weakened virus that can mutate and sometimes cause polio in patients or when it gets into sewage. Therefore, health experts now favor the injectable vaccine. "If we can do one-fifth the dose, we can at least get it down to $1, so we are getting into the neighborhood of a price that may be affordable for developing countries in the future," says Dr. Roland Sutter of the World Health Organization. ❖

Medicine

Octagam Withdrawal Issued for All Lots

Octapharma USA has initiated a voluntary wituhdrawal of all lots of Octagam (immune globulin intravenous [human] 5% liquid preparation) from the U.S. marketplace due to an unusually high number of thromboembolic events that have been associated with people being administered the drug. This follows an initial announcement in August of a voluntary withdrawal of selected lots of Octagam 5%, which reported at least nine events where blood clots dislodged and traveled through the body, causing injury and pain to patients.

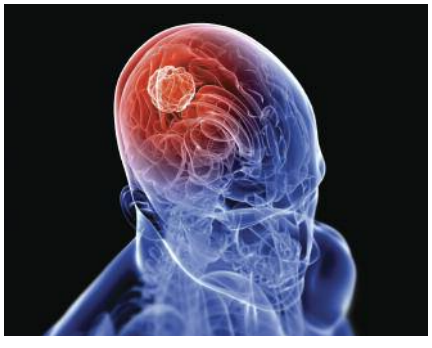
According to Octapharma USA, while the company has not received any reports of thromboembolic events since its initial voluntary market withdrawal, "the Food and Drug Administration and Octapharma agree that until a root cause analysis of the previously reported thromboembolic events can be determined, the most prudent course of action is to suspend further administration of Octagam 5%."

The company requests that customers quarantine all lots of Octagam 5% and then contact the Octapharma customer service department at (201) 604-1141 to return the product.

This withdrawal is for Octagam only. Octapharma's Albumin (Human) and Wilate, Von Willebrand Factor/Coagulation Factor VIII Complex (Human), are unaffected and are readily available in all sizes for purchase. ❖

Medicine

New Melanoma Drug May Destroy Brain Tumors



Bristol-Myers Squibb's biotechnology drug ipilimumab, which enlists the help of the immune system to attack tumors, has shown early promise for helping patients with advanced melanoma that has spread to the brain, according to a summary of data from a mid-stage study. Ipilimumab is a monoclonal antibody, an engineered human immune system protein that boosts the body's immune response by interfering with another immune compound called CTLA-4, which acts as a "brake" on immune system cells.

In the Phase II trial, the first to test ipilimumab in patients whose skin cancer had spread to the brain, four out of 51 patients with at least one brain lesion had a partial response to the drug, and in five out of 51 patients, both brain and other tumors in the body stabilized after 12 weeks of treatment. The responses lasted from three to 12 months, and patients had no serious toxic side effects. Data from a second study are still being evaluated.

A separate study of ipilimumab also showed signs that it could work in people who first appeared not to respond to the drug. Researchers reintroduced the drug to 32 patients who were initially treated as part of a study of 634 patients. Eight of the 32 got ipilimumab alone, 23 got ipilimumab plus a vaccine called gp100, and one got the vaccine alone. Patients whose cancer initially progressed while on ipilimumab and who were reintroduced to the drug had a disease control rate of 65 percent to 75 percent, compared with zero in the patient who got the vaccine only. ❖

Medicine

FDA Approves Prostate Cancer Drug

A first-of-its-kind prostate cancer treatment that uses the body's immune system to fight the disease has been approved by the U.S. Food and Drug Administration (FDA). Dendreon Corp.'s Provenge vaccine, which trains the immune system to fight tumors, is intended to treat cancer that has spread elsewhere in the body and is not responding to hormone therapy. Provenge is made by taking immune cells from a patient's blood and exposing them to a protein found in most prostate cancers, which encourages the cells to attack the cancer. It is given intravenously, with a total of three doses given approximately once every two weeks. Possible side effects include chills, fatigue, fever, back pain, nausea, joint ache and headache, according to the FDA. ❖

Vaccines

Rotavirus Vaccine Contraindicated for SCID Infants

According to the Centers for Disease Control and Prevention, the rotavirus vaccine is now contraindicated for infants diagnosed with severe combined immunodeficiency (SCID), and the organization is updating its contraindications list. This is in response to reported cases of vaccine-acquired rotavirus infection in infants with SCID following rotavirus vaccine administration. Merck & Co. and GlaxoSmithKline Biologics have revised their prescribing information and patient labeling for their respective rotavirus vaccine products, pentavalent rotavirus vaccine (RV5) and monovalent rotavirus vaccine (RV1), with approval from the U.S. Food and Drug Administration. ❖

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- IgA ≤25 mcg/mL

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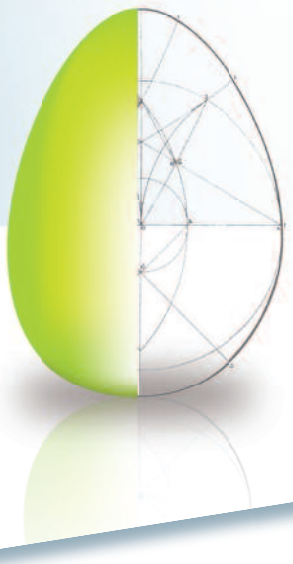
- In clinical trials, 97% of related adverse events were non-serious; 95% of 1038 infusions were administered without premedication. The most common adverse reactions were headache, pain, nausea, pyrexia/hyperthermia, fatigue, and chills
- 3-step virus inactivation/removal process, including nanofiltration to ~20 nanometers, reduces the risk of pathogen transmission



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Important Safety Information

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

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

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

Privigen is manufactured by CSL Behring AG and distributed by CSL Behring LLC.
Privigen is a registered trademark of CSL Behring AG.

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www.CSLBehring-us.com **www.Privigen.com** 09-PVG-051 4/2010

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

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

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

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

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

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

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

5.8 Volume Overload

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

5.9 Transmissible Infectious Agents

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

5.10 Monitoring: Laboratory Tests

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

5.11 Interference With Laboratory Tests

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Treatment of Primary Humoral Immunodeficiency

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

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

total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule. Of the 1038 infusions, 435 were administered to females and 603 to males.

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). This is below the target of 40% for this safety endpoint. The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2 lists the temporally associated AEs that occurred in more than 5% of subjects during a Privigen infusion or within 72 hours after the end of an infusion, *irrespective of causality*.

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

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

*Excluding infections.

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be related to the infusion of Privigen (including 5 serious, severe AEs described below). Of the 187 non-serious AEs related to the infusion of Privigen, 91 were mild, 81 were moderate, 14 were severe, and 1 was of unknown severity. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (29% of subjects), pain (14% of subjects), nausea (11% of subjects), fatigue (11% of subjects), and chills (11% of subjects).

Sixteen subjects (20%) experienced 41 serious AEs. Five of these were related severe AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature) that occurred in one subject and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative direct antiglobulin test (DAT) at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of 20 x 10^9/L or less received a total of 2 g/kg dose of Privigen administered as 1 g/kg intravenous infusions daily for 2 consecutive days (*see Clinical Studies [14.2]*). Subjects ranged in age from 15 to 69; 59.6% were female and 40.4% were male.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 3 lists the temporally associated AEs that occurred in more than 5% of subjects with chronic ITP during a Privigen infusion or within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen, *irrespective of causality*.

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

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

* Two consecutive daily infusions.

Of the 183 temporally associated AEs reported for the 57 subjects with chronic ITP, the investigators judged 150 to be related to the infusion of Privigen (including the one serious AE described below). Of the 149 non-serious AEs related to the infusion of Privigen, 103 were mild, 37 were moderate, and 9 were severe. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (65% of subjects) and pyrexia/hyperthermia (35% of subjects).

Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privigen.

One subject withdrew from the study due to gingival bleeding, which was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

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

Privigen Postmarketing Experience

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

General

The following mild to moderate reactions may occur with the administration of IGIV products: headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, skin reactions, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, myalgia, arthralgia, and changes in blood pressure. Immediate hypersensitivity and anaphylactic reactions are also a possibility.

The following adverse reactions have been identified and reported during the post-approval use of IGIV products.[12]

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Use of Privigen in nursing mothers has not been evaluated.

8.4 Pediatric Use

Treatment of Primary Humoral Immunodeficiency

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

Treatment of Chronic Immune Thrombocytopenic Purpura

Safety and effectiveness of Privigen have not been established in pediatric patients with chronic ITP who are under the age of 15.

8.5 Geriatric Use

Clinical studies of Privigen did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

Use caution when administering Privigen to patients age 65 and over who are judged to be at increased risk of developing renal insufficiency (*see Boxed Warning, Warnings and Precautions [5.2]*). Do not exceed recommended doses, and administer Privigen at the minimum infusion rate practicable.

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Based on November 2009 revision.

People and Places in the News

FDA APPROVALS

Talecris has been granted orphan drug designation by the Food and Drug Administration for the development of an aerosol formulation of Alpha1-Proteinase Inhibitor (Human, A1PI) to treat congenital alpha1-antitrypsin (AAT) deficiency.

CSL Behring has received FDA approval to extend the shelf life for Privigen, immune globulin intravenous (human), 10% Liquid from 24 months to 36 months. The approval makes Privigen the first liquid IVIG in the U.S. that can be stored at room temperature throughout its entire 36-month shelf life.

Phadia has received FDA 510 (K) clearance for four new EliA autoimmune antibody assays — anti-cardiolipin (aCL) IgG/IgM and anti-B2-glycoprotein 1 (anti-B2-GP1) IgG/IgM — that will provide physicians with additional tools needed to aid in the diagnosis of antiphospholipid syndrome (APS).

The FDA approved marketing authorization for **Sanofi-aventis**' Jevtana Injection in combination with prednisone for the treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing treatment regimen.

APPOINTMENTS

Theresa Wrangham, immediate past president of SafeMinds, has been appointed executive director of the National Vaccine Information Center.

CEO and Co-Founder of Lifetree Clinical Research and Lifetree Center for Neuroscience Research **Alice Jackson** has been named to the board of directors for the Alzheimer's Association, Utah Chapter.

John Maraganore, PhD, CEO, of Alnylan Pharmaceuticals, has been appointed to Taligen Therapeutics' board of directors. Taligen is a biotechnology company developing therapies that regulate the complement system to treat inflammatory and immune diseases.

Idera Pharmaceuticals has appointed three new executives to the staff of the Cambridge-based autoimmune disease drug developer. **Rober Arbeit** is vice president of clinical development, **Nicola La Monica** is vice president of biology, and **Timothy Sullivan** is vice president of development programs and alliance management.

Nutra Pharma Corp., a biotechnology company that is developing treatments for adrenomyeloneuropathy (AMN), HIV and multiple sclerosis, has hired **David Isserman** to serve as its chief marketing officer.

Richard Hockins has been appointed vice president of sales and marketing at Hycor Biomedical, a manufacturer of in vitro diagnostic products for allergy, autoimmune and urinalysis markets.

Biologics Consulting Group, a regulatory affairs consulting firm, has appointed **Craig A. Halverson**, MS, as a senior consultant. Halverson was previously vice president of regulatory affairs at Zymogenetics, which supported multiple investigational new drugs in hemostasis, oncology, immunology and infectious disease.

Tanabe Research Labs USA Inc. (TRL) has opened a facility in San Diego to develop biological drugs for the treatment of autoimmune diseases. TRL commenced operations in May with the appointment of three new senior executives, **Masaki Yamada**, PhD, chief executive officer; **Toshihiro Hosaka**, PhD, senior vice president; and **Roland Newman**, PhD, vice president and chief scientific officer.

ACQUISITIONS/ALLIANCES

Sanofi-aventis has completed its acquisition of **Chattem Inc.**, making it a wholly owned subsidiary of the Sanofi-aventis group. The move is intended to strengthen the company's presence in the U.S. consumer market and provide new channels for maximizing the potential of converting Sanofi-aventis' prescription medicines to over-the-counter products, beginning with Allegra.

Talecris Biotherapeutics has signed a co-promotion agreement with **Novartis Vaccines** to jointly market and sell their respective post-exposure rabies products. Talecris provides HyeperRAB(R) S/D (rabies immune globulin [human]), which is administered in combination with rabies vaccines. Novartis provides RabAvert(R) rabies vaccine for both pre-exposure and post-exposure prophylaxis.

Grifols SA has acquired various forms of intellectual property associated with the treatment of post-polio syndrome (PPS) from Swedish company **Pharmalink AB**. In addition, Grifols has acquired U.S., European and Japanese patents for a specific PPS treatment method utilizing human immunoglobulin and unrestricted use of existing Pharmalink clinical trial data supporting the treatment method.

Laboratory instruments and solutions provider **Tecan Group AG** has signed a global OEM agreement with the diagnostics business of **Novartis** to provide instruments that will be used to meet the needs of blood banks testing individual or pooled donations.

ZymoGenetics Inc. has signed a licensing agreement with Danish drug maker **Novo Nordisk A/S** for ZymoGenetics' autoimmune and inflammatory drug IL-21 mAb.

Viral Genetics Inc. has signed licensing

agreements for medical technology developed by **Karen Newell**, a University of Colorado at Colorado Springs associate biology professor. The company plans to seek FDA approval to begin testing a new type of drug that targets the response of an individual's immune system to fight off HIV, cancer, lupus, diabetes, rheumatoid arthritis and other autoimmune diseases.

Cornerstone Pharmaceuticals Inc. has entered into a collaboration agreement with the **U.S. National Cancer Institute** (NCI) to evaluate the potential of combining Cornerstone's proprietary Emulsiphan cancer selective delivery nanotechnology platform with NCI's class of agents that can be turned into toxic compounds by targeted radiation and ultrasound to reduce tumors.

Inspiration Pharmaceuticals Inc. and **Ipsen SA** are merging their hemophilia portfolios. Ipsen will fund clinical development of its two lead products, and Inspiration will handle the work.

MediConnect Global, a player in the electronic medical records industry, has acquired the personal health record Internet portal **PassportMD**, and has changed the program's name to myMediConnect.

Calgene Corp. has acquired **Abraxis BioScience**, adding Abraxane for Injectable Suspension to Calgene's existing portfolio of leading cancer products. Abraxane was approved by the FDA in January 2005 for the treatment of breast cancer after failure of combination chemotherapy.

AWARD

Taligen Therapeutics has been selected as the **Bioscience Company of the Year** by the University of Colorado with its 7th Annual Technology Transfer Awards in recognition of its leadership position in developing a pipeline of novel protein therapeutics that modulate the complement system to treat a wide range of inflammatory diseases.

GRANTS/DONATIONS

Privately owned Immune Targeting Systems has secured an additional $13.6 million of funding from a group of investors that includes the venture capital arm of Novartis to develop its **universal flu vaccine** to protect people against all flu strains by targeting elements of the virus that do not change from season to season. The funding will allow the company to progress its lead candidate FP-01 through to completion of Phase II proof of concept studies. Initial Phase I clinical trials started in early 2010.

Inovio and collaborators from Drexel University, Cheyney University and the University of Pennsylvania received a $2.8 million grant to develop a DNA vaccine to treat the **hepatitis C** virus.

The National Institutes of Health has awarded a $600,000 grant to Corgenix for a two-year study to develop novel, recombinant-based diagnostic tests for the **Ebola** and **Marburg** viruses.

Dr. Jean Pfau, an assistant professor of biological sciences at Idaho State University, has received a $192,000 grant from the National Institutes of Health to research the effects of **asbestos** on healthy cells.

Vical Inc. is collaborating with leading pediatric infectious disease researchers Stuart P. Adler, MD, and Michael A. McVoy, PhD, of the Virginia Commonwealth University under a five-year, $4 million grant from the National Institute of Allergy and Infectious Diseases to support development and animal testing of novel vaccine approaches designed to protect women of child-bearing age from infection with **cytomegalovirus** (CMV).

Researchers at the **University of Cincinnati Interstitial Lung Disease Center** have received a $715,000 K23 clinical research grant from the National Heart, Lung and Blood Institute to study ways ILD first appears in certain patient groups with autoimmune diseases and how to more efficiently diagnose and treat it.

Kineta Inc. has received a $600,000, two-year Phase I Small Business Innovation Research grant to finance its IND-enabling studies of ShK-186, the first-in-class therapeutic for **type 1 diabetes mellitus**, **multiple sclerosis** and other **autoimmune diseases**.

The **California Institute for Regenerative Medicine**, the state's stem cell research funding agency, has awarded $25 million to 19 projects, including nearly $13.9 million for 11 San Francisco Bay-area projects dealing with immune rejection of transplanted stem cells. Among those 11 projects are $1.4 million to Escape Therapeutics Inc., more than $2 million to University of California, Berkeley, researchers, and $3.8 million to University of California, San Francisco, researchers.

CLINICAL TRIALS

Grifols, SA, will initiate a new clinical investigation of **Alzheimer's** disease in January 2011 that will involve a combined treatment of therapeutic plasmapheresis and the administration of human albumin and intravenous immune globulin at different doses and frequencies.

Medicago Inc., a small Canadian biotechnology company, began mid-stage trials of its **H5N1 avian flu vaccine** in mid-2010, following positive results of its Phase I clinical trial.

Upsher-Smith Laboratories has initiated a global Phase III clinical trial for USL255 (extended-release topiramate), an internally developed program for the management of **epilepsy** in adults. ❖

Disease

Whooping Cough Outbreaks Increase

In June, the state of California declared an epidemic of whooping cough (pertussis) with 910 confirmed cases, making it possible that California will have the largest whooping cough outbreak in 50 years. As of that time, five people had died of whooping cough in California, all of them Latino babies under the age of 3 months old. Symptoms of whooping cough are a common cold, followed by a cough that doesn't go away for weeks or months, and can sometimes result in a whooping sound. (See the related story on page 49.)

According to public health officials, the whooping cough vaccine can wear off after five years, so they are encouraging older children to be revaccinated. They also are warning Californians to

get their vaccinations as soon as possible because the illness is highly contagious. Babies are normally vaccinated with the DTap vaccine for whooping cough several times during their first year of life, and additional rounds are recommended at between 15 and 18 months, and again between ages 4 and 6. ❖

Vaccines

New Meningitis Vaccine Could Prevent Outbreaks

A new meningitis vaccine will help to prevent epidemics in Africa for the first time, revolutionizing how doctors fight outbreaks of the deadly disease, say health officials. Recently approved by the World Health Organization (WHO), the vaccine targets type A meningitis, which causes more than 90 percent of outbreaks in Africa. The vaccine is the result of a partnership that began in 2001 between the WHO, the Serum Institute of India and PATH, an international non-profit funded by the Bill and Melinda Gates Foundation. It costs 40 cents a shot, and UNICEF can now purchase the vaccine for countries. ❖

Medical Product

Blood Test Could Provide Early Cancer Detection

A new blood test that will aid the detection of cancer as much as five years earlier than current testing methods, such as mammography and CT scans, has been developed by Oncimmune Ltd., a University of Nottingham (England) spin-out company. The commercial test uses immune-biomarkers, and replicates the cancer proteins that trigger the body's response to the disease, as well as robotic technology to measure that response.

This science is based on the early work of John Robertson, a world-renowned breast cancer specialist and professor of surgery in the University of Nottingham's Faculty of Medicine and Health Sciences. Initial research results were derived using blood samples from patients with breast cancer and a group of high-risk women attending for annual mammography. In addition to identifying the signal in the blood of a percentage of women when they developed breast cancer, the results showed that the signal could be detected in some of the high-risk patients who had given blood samples for a number of years during their annual checkup and before they were subsequently diagnosed with cancer. When these samples were run retrospectively, it showed that the prototype assay test could have detected more than half of these cancers up to four years before they were actually diagnosed. A study involving researchers at the Mayo Clinic in the U.S. recorded similar results using blood samples from a study of CT scans to screen for lung cancer where antibodies were detected up to five years before the lung cancers were diagnosed.

Oncimmune has transferred this science into a commercial test. The test for lung cancer, EarlyCDT-Lung, was launched nationally in the U.S. in June, and it will be followed by a launch in the United Kingdom in 2011. Tests for other cancers will launch in the next few years. ❖

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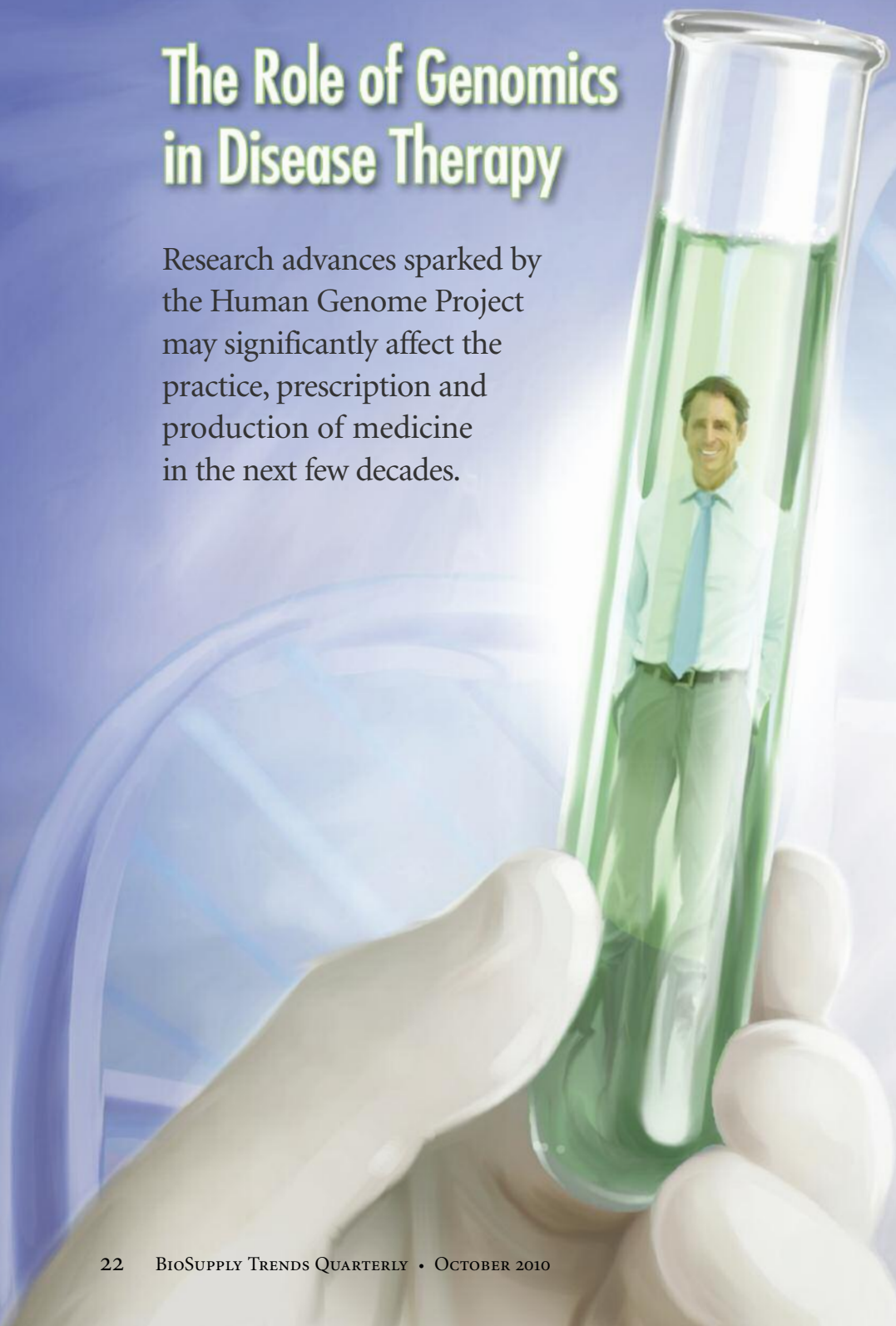
Personalized Medicine

The Role of Genomics in Disease Therapy

Research advances sparked by the Human Genome Project may significantly affect the practice, prescription and production of medicine in the next few decades.



By Trudie Mitschang

In 1990, the United States Department of Energy and the National Institutes of Health began a comprehensive study titled the Human Genome Project (HGP).[1] The 13-year study endeavored to understand the genetic makeup of human beings, and its completion spawned an entirely new field of study called "genomics." This field of study has had significant influence on the medical community, impacting resources, knowledge and technology surrounding genetic contributions to human health. Because of the HGP, genetics is playing an increasingly important role in the diagnosis, monitoring and treatment of diseases, and the development and prescription of medication.

The History of Genetic Study

Scientists first began an in-depth study of genetics in the early 20th century by applying the plant-based research of Austrian monk Gregor Mendel to the study of human genetics. In 1905, W.C. Farrabee, an anthropologist at Yale University, published a study that described a family with brachydactyly, a dominant genetic disorder in which affected people have very short and stubby fingers. This was the first published scientific report to document the inheritance pattern of genetic disease.[2]

The past few decades have seen the rapid advancement of genetic testing capabilities, leading to breakthroughs in drug development, disease diagnosis and preventive medical care.

The discovery of genetic links to disease eventually led scientists to wonder if social and personality traits were genetically influenced as well, which led to a field of study called "eugenics." Eugenics focused on how to predict and influence traits like intelligence, criminal behavior, poverty and artistic ability through the study of dominant or recessive genes. However, eugenics took a dark turn in the 1930s when Nazis took the concept to the extreme and attempted to rid the world of anyone deemed "genetically impure." While mainstream eugenics was more or less abandoned after World War II, many scientists and physicians remained interested in genetic study and the role that heredity plays in diseases and birth defects. As a result, the first medical genetics clinics opened in the United States in the mid-1940s and early 1950s.

Around 1950, a number of discoveries were made regarding the nature of DNA and the structure of the DNA molecule. In 1975, a method to isolate and analyze DNA fragments now known as the Southern blot analysis was discovered and used in genetic testing. By the early 1980s, improved testing techniques helped researchers discover genetic links to disorders like cystic fibrosis, muscular dystrophy and Huntington's disease.

The past few decades have seen the rapid advancement of genetic testing capabilities, leading to breakthroughs in drug development, disease diagnosis and preventive medical care.

The Emerging Field of Pharmacogenomics

A relatively new area of genetic study focuses on tailoring drugs to an individual's genetic makeup. Known as pharmacogenomics, this emerging science already is used for several commonly prescribed drugs. Recently, two large prescription drug companies announced plans to offer in-pharmacy genetic testing as part of the prescription-filling process. In effect, certain prescriptions will trigger physician notification about available genetic testing, which will then be offered as an option to the patient. Presumably, the testing will help physicians customize prescriptions to fit individual needs, ward off undesirable side effects and optimize patient outcomes.

"There are still a relatively small number of drugs where pharmacogenomics actually plays a role, but this could drastically expand over the next five years," says Scott Weiss, a physician at Harvard Medical School and interim director of the Partners HealthCare Center for Personalized Genetic Medicine. "Antidepressants, asthma meds, anti-arrhythmia drugs, lipid-lowering drugs — some of the biggest sellers in terms of drug use nationally could potentially have pharmacogenetic implications."[3]

Diagnosing and Predicting Disease

The knowledge garnered from the HGP has helped researchers better understand some of the genetic influences that cause or contribute to disease. All diseases have a genetic component, whether inherited or as a result of the body's response to environmental stresses, such as viruses or toxins. Ultimately, the goal is to learn how a faulty gene might cause disease, and then use this information to treat, cure or even prevent various diseases. Of course, some information gathered from genetic testing is beneficial only from a research perspective; knowing you have a likelihood of developing an incurable disease like Alzheimer's offers little benefit. On the other hand, some testing in areas like dermatology may provide opportunity for preemptive treatment for common — albeit not life-threatening — inherited conditions, such as male and female pattern baldness.

A relatively new area of genetic study focuses on tailoring drugs to an individual's genetic makeup.

"Current genetic testing can predict with 80 percent accuracy whether an individual will lose their hair. We can also test patients to see how they will respond to various interventions, saving them the expense and emotional distress associated with ineffective treatments," says Andy Goren, president and chief executive officer of HairDX, a pharmacogenomics company in Irvine, Calif.

While science is still in the early stages of understanding the genetic link to disorders such as hair loss, certain genes have been identified as a predetermining factor in assessing the likelihood of early-onset baldness. And, since effective medical treatments are available to treat hair loss, identifying this gene in an individual can be beneficial from a clinical perspective. In the future, lessons learned from this type of genetic testing can potentially help patients and physicians better understand the implications of genetic testing for more complex health concerns, especially as such testing becomes more widely available.[1]

Gene Therapy and Drug Design

Thanks in large part to breakthroughs in genetic studies, research and development of future pharmaceuticals are shifting away from diagnostics and toward developing new-generation therapeutics based on genes. This opens the door for entire new classes of medicines based on gene sequence and protein structure, as opposed to traditional trial-and-error methods.

The potential for using genes themselves to treat disease is another exciting application of DNA science. This rapidly developing field holds great potential for treating or even curing genetic and acquired diseases by using normal genes to replace or supplement a defective gene or to bolster immunity to disease. In recent studies, gene therapy has been used successfully to cure deafness in guinea pigs, to restore vision in dogs and to reduce the size of human lung cancer tumors in mice.[4]

Ethical Issues Remain

The amount of gene-related research and development occurring in the United States continues to grow at a fast rate, as do certain ethical, medical and social concerns. Proponents of genetic testing to predict disease argue that genetic-risk information should be viewed just like any other risk information, such as high cholesterol levels, and that consumers have a right to that information. Opponents argue that the testing is not clinically proven and can be difficult to interpret; an individual with a 75 percent chance of developing a particular genetic disease may remain healthy throughout his or her life, while an individual with only 25 percent probability of disease development may end up succumbing to it. Privacy issues related to employment and qualification for health insurance also come into play.

Still Moving Forward

The U.S. Food and Drug Administration is currently fielding numerous requests from medical researchers and manufacturers to study gene therapy and to develop gene therapy products. Such research could lead to gene-based treatments for cancer, cystic fibrosis, heart disease, hemophilia, wounds, infectious diseases such as AIDS, and graft-versus-host disease. ❖

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

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

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

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

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

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

Please see brief summary of full Prescribing Information on next page.

Reference: 1. Data on file. CSL Behring LLC.

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

1 INDICATIONS AND USAGE

1.1 Hemophilia A

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

1.2 Von Willebrand Disease (VWD)

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

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

IU = International Units.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Events (VWD Patients)

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

5.2 Monitoring for Intravascular Hemolysis

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

5.3 Monitoring VWF:RCo and FVIII Levels

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

5.4 Transmission of Infectious Agents

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

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

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

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Studies Experience

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

Treatment of Bleeding Episodes in VWD

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

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

Prevention of Excessive Bleeding During and After Surgery in VWD

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

Table 5: Hemorrhagic Adverse Events in 63 Surgical Subjects

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

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

7 DRUG INTERACTIONS

None reported.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Hemophilia A

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

VWD

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

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

8.5 Geriatric Use

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

15 REFERENCES

3. Mannucci, PM. Venous Thromboembolism in Von Willebrand Disease. *Thromb Haemostas.* 2002;88:378-379.
4. Markis M, Colvin B, Gupta V, Shields ML, Smith MP. Venous thrombosis following the use of intermediate purity FVIII concentrate to treat patients with von Willebrand's disease. *Thromb Haemostas.* 2002;88:387-388.

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THE NEW HIGH-DOSE FLU VACCINE: AN EXTRA BOOST FOR SENIORS

By Keith Berman, MPH, MBA, and Luke Noll

New research comparing the new Fluzone High-Dose vaccine and the seasonal flu vaccine sheds light on how ineffective the latter vaccine has been for the elderly.

"Old age is no place for sissies," the film actress Bette Davis observed late in her life while lying in a hospital bed. When this year's influenza season comes around, Americans over age 65 will be gently reminded of this fact as they're urged and prodded to get their annual flu shot. And, more than two-thirds of seniors do so these days — not the 90 percent that public health experts have called for, but a lot better than the woefully low 30 percent vaccination rate in this age group just 20 years ago.[1]

People over 65 years of age, and particularly those well beyond 65, are hit especially hard by seasonal influenza. In fact, in this age group, a case of the flu is most likely to lead to serious or life-threatening complications, especially in those

with chronic pre-existing conditions, such as cardiac and pulmonary disease. In the elderly in particular, a bout of the flu also can progress to primary influenza pneumonia or secondary bacterial pneumonia.

Each year, seniors account for an estimated 46 percent of all flu-related clinic visits, nearly 60 percent of all annual flu-related hospital days, three-quarters of life-years lost (Table 1)[2] and 90 percent of this country's estimated 36,000-41,000 annual flu-related deaths. And, while the seasonal flu vaccine has been said to protect this group from contracting the flu, new research suggests that this has not been the case. But, with a new high-dose flu vaccine now on the market, the elderly will likely be much better protected from the flu.

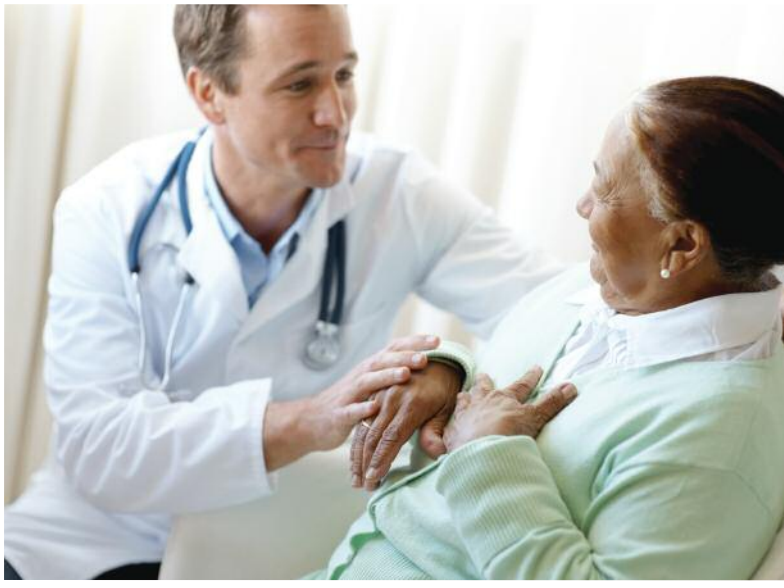
Getting TIV, Getting the Flu

With more than a doubling of the vaccination rate since 1990, one would expect a healthy drop in flu-related hospitalizations and deaths. But those numbers haven't dropped. In fact, overall hospital admission and death rates in the U.S. have actually increased over the last two decades,[3] even after accounting for changing age demographics and ups and downs in this customized vaccine's effectiveness against each season's new flu strain.

The actual life- and health-sparing value of flu vaccine in the elderly has been a subject of some controversy.

The actual life- and health-sparing value of flu vaccine in the elderly has been a subject of some controversy. Nearly all the evidence for protective benefit in this population comes from non-randomized observational studies. Typical of these was a large 2003 medical record review of 286,000 community-dwelling Americans at least 65 years old. In this review, those who got a flu vaccine experienced nearly a 20 percent reduction in risk of hospitalization for cardiac disease, about a 30 percent lower risk of hospitalization for pneumonia or influenza, and an impressive 49 percent average reduction in risk of death from all causes over the span of two flu seasons.[4]

But many experts have pointed out



the strong potential for bias when studies look at health outcomes in people who choose themselves whether to get a flu vaccine or not. One research team decided to take a closer look at the issue. They followed a large cohort of 72,527 people aged 65 and older during an eight-year period to assess the risk of death or hospitalization for pneumonia or the flu before, during and after flu seasons.[5] Their findings have all but discredited the rosy results of earlier "observational" flu studies in seniors. Before the flu season even arrived, the relative risk of death for vaccinated persons compared to unvaccinated persons was 0.39. In other words, people who lined up for their flu shot were about 60 percent less likely to die from any cause compared with those who didn't — before they received the vaccine or got exposed to the new flu virus!

This obvious bias is built into any study that simply tallies deaths or hospitalizations of people who decided on their own whether to get a flu shot. People who choose on their own to get the vaccine clearly tend to be much healthier than those who don't, and they appear to take better care of themselves when they do get sick.

Table 1. Estimated annual burden of influenza in the U.S. by age group

Age (years)	Outpatient visits	Hospital days	Life years lost
<5	3,728,000	280,000	11,000
5-17	3,718,000	22,000	3,000
18-49	5,270,000	305,000	36,000
50-64	4,329,000	717,000	92,000
65+	14,309,000	1,807,000	468,000
All ages	31,354,000	3,131,000	611,000

The underlying answer to the paradox of more flu-related deaths despite higher vaccination rates in the elderly is straightforward: Standard trivalent inactivated influenza vaccine (TIV) isn't nearly as protective for older adults as it is for non-elderly adults. After age 65, the competency of our immune system steadily declines with passing years. Sooner or later, this natural course of "immunosenescence" translates to a poor, nonprotective antibody response to the standard dose of influenza vaccine.[6] It also accounts for why people 85 years of age and older are roughly 16 times more likely to die of any flu-related cause and more than 30 times more likely to die of influenza or associated pneumonia than those between age 65 and 69.[7]

The overall chances that elderly persons will have a potentially protective antibody response to flu vaccine has been estimated to be somewhere between 24 percent and 59 percent of that of younger adults. According to U.S. Centers for Disease Control and Prevention (CDC) estimates, healthy adults under age 65 can expect a 70 percent to 90 percent overall clinical vaccine efficacy rate when the vaccine and circulating virus are antigenically similar. But the clinical efficacy of flu vaccine is clearly far lower in the elderly.[8]

The underlying answer to the paradox of more flu-related deaths despite higher vaccination rates in the elderly is straightforward: Standard trivalent inactivated influenza vaccine (TIV) isn't nearly as protective for older adults as it is for non-elderly adults.

As flu experts have pointed out for decades, what is needed is a more immunogenic flu vaccine for the elderly, one that more consistently and effectively mobilizes their available antibody and cellular immunity.

Table 2. Immunogenicity of Fluzone High-Dose and standard TIV in a randomized trial of adults 65 years of age and older[a]

Seroconversion:b

	Fluzone High-Dose	Standard TIV
Strain	(% of subjects)	(% of subjects)
A/H1N1	48.6%	23.1%
A/H3N2	69.1%	50.7%
B	41.8%	29.9%

Seroprotection:b

	HA inhibition	Fluzone High-Dose	Standard TIV
Strain	titer	(% of subjects)	(% of subjects)
A/H1N1	HAI ≥ 1:40	89.9%	76.8%
	HAI ≥ 1:80	73%	51%
	HAI ≥ 1:160	45%	26%
A/H3N2	HAI ≥ 1:40	99.3%	96.5%
	HAI ≥ 1:80	97%	89%
	HAI ≥ 1:160	91%	78%
B	HAI ≥ 1:40	79.3%	67.6%
	HAI ≥ 1:80	52%	39%
	HAI ≥ 1:160	22%	16%

a. All differences statistically significant
b. Seroconversion defined as prevaccination titer <1:10 and post-vaccination titer ≥1:40, or a ≥4-fold increase from day 0 to day 28

This Flu Season's New Arrival: Fluzone High-Dose

For the first time since the flu vaccine's introduction in the 1940s, Americans aged 65 and older will have the option of receiving a high-potency flu vaccine during the current 2010-2011 season.

Last December's U.S. Food and Drug Administration (FDA) approval of Sanofi Pasteur's Fluzone High-Dose (Fluzone HD) proves once again that sometimes successful ideas also are the simplest ones. Instead of the 15 micrograms (mcg) of each of the three hemagglutinin viral surface antigens included in standard TIV preparations, Fluzone HD delivers 60 mcg — four times as much — in the same 0.5 mL dose for intramuscular injection. A different colored syringe plunger distinguishes it from regular Fluzone provided in a prefilled syringe. Everything else about the two products is the same.

Immunogenicity findings from three

clinical trials in persons 65 years of age and older demonstrate that Fluzone HD elicits substantially higher hemagglutinin inhibition (HI) titers than the standard dose.[9,10,11] In the largest of these studies, the mean post-vaccination antibody titer elicited by Fluzone HD against the A/H1NI, A/H3N2 and B flu strains was 70 percent, 80 percent and 30 percent higher, respectively, than the titer elicited by the standard-dose vaccine. Additional important evidence of the enhanced immunogenicity of Fluzone HD is revealed by comparative seroconversion and seroprotection findings, as summarized in Table 2.

In studies over the last 40 years, higher HI titers have been shown to directly correlate with lower rates of influenza infection.[12,13,14] To the extent that higher post-vaccination HI titers are predictive for increased protective immunity in older adults, there is every reason to hope and expect that Fluzone HD can reduce the frequency of laboratory-confirmed flu and its serious complications.

More Injected Vaccine Antigen, More Transient Reactions

With four times as much hemagglutinin antigen (HA) being introduced into the muscle tissue as the same volume of traditional flu vaccine, more injection site and systemic reactions are to be expected. This is exactly what was observed in a pivotal trial involving 2,573 subjects aged 65 years and older who were administered Fluzone HD and 1,260 subjects who were given Fluzone. Table 3 summarizes these adverse event findings.[15] Most of these local and systemic reactions were mild and resolved within three days. However, significantly more Fluzone HD recipients (1.1 percent) reported moderate to severe fever than those who received standard Fluzone (0.3 percent).[16]

The more important comparative measure — the rate of serious adverse events — was not found to be different between subjects who received the high-dose (156/2573; 6.1 percent) and standard (93/1260; 7.4 percent) Fluzone products.

No one looks forward to a higher likelihood of injection site reactions, transient headaches, fever and the like. But, there is an upside: Along with increased anti-HA antibody titers, a higher frequency of these events signals a more active and potentially more protective immune response.

Better Protection Against the Flu?

As noted earlier, better HI antibody responses are known to correlate with protection against influenza infection and reduced clinical disease risk. Yet while it is very encouraging that Fluzone HD induces higher serum antibody titers without significant safety concerns, the jury is still out on whether this actually translates into fewer confirmed cases and serious complications from the flu.

As a condition of licensure under FDA's "accelerated approval" process, the agency instructed Sanofi Pasteur to conduct a head-to-head study to compare Fluzone HD and Fluzone (the "active control") in 27,000 to 30,000 adult subjects 65 years of age and older. That study will be conducted over three flu seasons to try to account for typical fluctuation in vaccine efficacy, which is related to differences between the flu virus that arrives and the strains picked in advance to make the vaccine. The first season (2009-2010) is

Table 3. Frequency of solicited injection site and systemic adverse events within seven days post-vaccination

	Fluzone High-Dose	Fluzone
Injection site reactions		
Pain	35.6%	24.3%
Erythema	14.9%	10.8%
Swelling	8.9%	5.8%
Systemic adverse events		
Myalgia	21.4%	18.3%
Malaise	18.0%	14.0%
Headache	16.8%	14.4%
Fever	3.6%	2.3%

Fluzone High-Dose vaccine was designed specifically to generate a more robust immune response to influenza in patients 65 years of age and older[1,2]

Fluzone® High-Dose
INFLUENZA VIRUS VACCINE

Fluzone High-Dose vaccine:

- Generates up to 80% higher antibody levels compared to standard-dose Fluzone vaccine[1,2,a]
- Is a covered benefit under Medicare Part B[b]
- The ACIP[c] included Fluzone High-Dose vaccine among the vaccines recommended for adults 65 years of age and older in its 2010-2011 annual influenza prevention recommendations[3]

[a] There are no data demonstrating clinically relevant prevention of culture-confirmed influenza or its complications after vaccination with Fluzone High-Dose vaccine compared to standard-dose Fluzone vaccine in individuals 65 years of age and older.

[b] If you have further questions regarding reimbursement, please call **1-800-VACCINE** (1-800-822-2463).

[c] ACIP=Advisory Committee on Immunization Practices.

Order your doses of Fluzone High-Dose vaccine today.
Log onto MyFluVaccine.com or call (800) 843-7477.

Indication

Fluzone High-Dose vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. This indication is based on the immune response elicited by Fluzone High-Dose vaccine; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose vaccine.

Safety Information

The most common local and systemic adverse reactions to Fluzone High-Dose vaccine include soreness, pain, and swelling at the vaccination site; fever, headache, malaise, and myalgia. Other adverse reactions may occur. Fluzone High-Dose vaccine should not be administered to anyone with a history of hypersensitivity to any vaccine component, including eggs, and egg products. The decision to give Fluzone High-Dose vaccine should be based on the potential benefits and risks, especially if Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine. The tip caps of the prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals. Vaccination with Fluzone High-Dose vaccine may not protect all individuals.

Before administering Fluzone High-Dose vaccine, please see brief summary of full Prescribing Information on following page.

Fluzone High-Dose vaccine is manufactured and distributed by Sanofi Pasteur Inc.

References: 1. Fluzone Vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2009. **2.** Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis.* 2009;200:172-180. **3.** Centers for Disease Control and Prevention. ACIP provisional recommendations for the use of influenza vaccines. http://www.cdc.gov/vaccines/recs/provisional/downloads/flu-vac-mar-2010-508.pdf. Accessed April 22, 2010.

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The vaccines division of sanofi-aventis Group

Fluzone® High-Dose Influenza Virus Vaccine

2010-2011 Formula

℞ only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE

Fluzone High-Dose is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. This indication is based on the immune response elicited by Fluzone High-Dose; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose.

DOSAGE AND ADMINISTRATION

Dosage and Schedule

Basic dosing information for Fluzone High-Dose, and its respective age indication, is presented in Table 1.

Table 1: Fluzone High-Dose

Any vaccination status	Dose/Route	Schedule
65 years and older	0.5 mL/ Intramuscular	1 dose

Administration

Inspect Fluzone High-Dose syringes visually for particulate matter and/or discoloration prior to administration. If either of these conditions exist, the vaccine should not be administered. Shake the syringe before administering the vaccine. The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk. For needle length, refer to the Advisory Committee on Immunization Practices (ACIP) recommendations.[1] If Fluzone High-Dose is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at separate injection sites.

Adults 65 years of age and older

Fluzone High-Dose should be administered as a single intramuscular dose preferably in the deltoid muscle.

DOSAGE FORMS AND STRENGTHS

Fluzone High-Dose

Sterile suspension for intramuscular injection supplied in prefilled syringes, 0.5 mL, for adults 65 years of age and older, distinguished by a gray syringe plunger rod.

Each 0.5 mL dose of Fluzone High-Dose contains influenza split virus antigens that are formulated to contain a total of 180 mcg of influenza virus hemagglutinin, 60 mcg each from the 3 influenza virus strains in the vaccine.

CONTRAINDICATIONS

Do not administer Fluzone High-Dose to anyone with a known hypersensitivity to egg proteins or any component of the vaccine, or life-threatening reactions after previous administration of any influenza vaccine.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone High-Dose should be based on careful consideration of the potential benefits and risks.

Altered Immunocompetence

If Fluzone High-Dose is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. The tip caps of the Fluzone High-Dose prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Limitations of Vaccine Effectiveness

Vaccination with Fluzone High-Dose may not protect all recipients.

ADVERSE REACTIONS

Clinical Trial Experience

Fluzone High-Dose

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, active-controlled, double-blind trial conducted in the US. The safety analysis set included 2,573 Fluzone High-Dose recipients and 1,260 Fluzone recipients.

Table 2 summarizes solicited injection site and systemic adverse events collected within 7 days post vaccination via diary cards. Onset was usually within the first 3 days after vaccination and majority of the reactions resolved within 3 days.

Table 2: Frequency of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N^a= 2573) Percent	Fluzone (N^a= 1260) Percent
Injection site reactions		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
Systemic adverse events		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever	3.6	2.3

[a] N is the number of subjects in the Safety Analysis Set.

Solicited injection site reactions and systemic adverse events were more frequent after vaccination with Fluzone High-Dose compared to standard Fluzone in adults 65 years of age and older.

Table 3 summarizes the severity of solicited adverse events that occurred during the first week after vaccination[2]:

Table 3: Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N^a=2573) Percent	Fluzone (N^a=1260) Percent
Injection Site Pain		
Mild	31.5	22.5
Moderate	3.7	1.7
Severe	0.3	0.2
Injection Site Erythema		
Mild	11.3	9.4
Moderate	1.9	0.8
Severe	1.8	0.6
Injection Site Swelling		
Mild	5.8	3.9
Moderate	1.6	1.3
Severe	1.5	0.6
Myalgia		
Mild	15.6	14.8
Moderate	4.2	3.2
Severe	1.6	0.2
Malaise		
Mild	11.7	9.8
Moderate	4.7	3.7
Severe	1.6	0.6
Headache		
Mild	12.6	11.7
Moderate	3.1	2.5
Severe	1.1	0.3

Table 3 (continued): Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N^a=2573) Percent	Fluzone (N^a=1260) Percent
Fever		
Mild	2.5	2.0
Moderate	1.1	0.2
Severe	0.0	0.1

[a] N is the number of subjects in the Safety Analysis Set.

The rates of Serious Adverse Events (SAEs) were comparable between the two groups; 156/2573 (6.1%) of Fluzone High-Dose recipients and 93/1260 (7.4%) of Fluzone recipients experienced SAEs.

No deaths were reported within 28 days post-vaccination. A total of 23 deaths were reported during the follow-up period of the study; 16/2573 (0.6%) among Fluzone High-Dose recipients and 7/1260 (0.6%) among Fluzone recipients. The majority of these participants had a medical history of cardiac, hepatic, neoplastic, renal, and/or respiratory diseases.

Post-Marketing Experience

The following events have been reported during the post-approval use of Fluzone.

Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

- *Blood and Lymphatic System Disorders:* Thrombocytopenia, lymphadenopathy
- *Immune System Disorders:* Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- *Nervous System Disorders:* Guillain-Barré syndrome (GBS), convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- *Vascular Disorders:* Vasculitis, vasodilatation/flushing
- *Respiratory, Thoracic and Mediastinal Disorders:* Dyspnea, pharyngitis, rhinitis
- *Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson syndrome
- *General Disorders and Administration Site Conditions:* Pruritus, asthenia/fatigue, pain in extremities, chest pain

Other Adverse Events Associated with Influenza Vaccines

Anaphylaxis has been reported after administration of Fluzone and other influenza vaccines. Although Fluzone and Fluzone High-Dose contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have egg allergy. Allergic reactions include anaphylaxis, angioedema, hives, and asthma.

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

USE IN SPECIFIC POPULATIONS

Fluzone High-Dose

Pediatric Use: Safety and effectiveness of Fluzone High-Dose in children have not been established.

Geriatric Use: Fluzone High-Dose is indicated for adults 65 years of age and older.

CLINICAL STUDIES

Immunogenicity of Fluzone High-Dose in Adults 65 Years of Age and Older

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, randomized, active-controlled, double blind trial conducted in the US. Of those, 3,851 (2,576 randomized to Fluzone High-Dose and 1,275 randomized to Fluzone) were included in the immunogenicity analysis according to the vaccine they were randomized to receive.[2]

The primary endpoint of the study was HI titer 28 days after vaccination. Pre-specified statistical superiority criteria required that (1) the lower limit (LL) of the 2-sided 95% CI of the GMT ratio [Fluzone High-Dose/Fluzone] be greater than 1.50 for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>0.67), and that (2) the lower limit of the 2-sided 95% CI of the seroconversion rate difference [Fluzone High-Dose - Fluzone] be greater than 10% for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>-10%). As shown in Table 4, statistically superior HI titers after vaccination with Fluzone High-Dose compared to standard dose Fluzone were demonstrated for two of the three influenza strains. There are no data demonstrating clinically relevant prevention of culture-confirmed influenza or its complications after vaccination with Fluzone High-Dose compared to standard dose Fluzone in individuals 65 years of age and older.

Table 4: GMT Ratios and Seroconversion Rates Following Vaccination with Fluzone High-Dose

	GMT		GMT Ratio	Seroconversion %[a]		Difference	Met Both Pre-defined Endpoints?[c]
Influenza Strain	Fluzone High-Dose N^b=2576	Fluzone N^b=1275	Fluzone High-Dose over Fluzone (95% CI)	Fluzone High-Dose N^b=2576	Fluzone N^b=1275	Fluzone High-Dose minus Fluzone (95% CI)	
A (H1N1)	115.8	67.3	1.7 (1.6; 1.8)	48.6	23.1	25.4 (22.4; 28.5)	Yes
A (H3N2)	608.9	332.5	1.8 (1.7; 2.0)	69.1	50.7	18.4 (15.1; 21.7)	Yes
B	69.1	52.3	1.3 (1.2; 1.4)	41.8	29.9	11.8 (8.6; 15.0)	No

Note: As defined in the study protocol:

[a] Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (day 28) titer ≥1:40 or a 4-fold increase for those with pre-vaccination titer ≥1:10.

[b] N is the number of subjects in the Immunogenicity Analysis Set.

[c] Predefined superiority endpoint for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (Fluzone High-Dose minus Fluzone) is >10%. Predefined superiority endpoint for GMT ratio: the lower limit of the 95% CI for GMT ratio (Fluzone High-Dose divided by Fluzone) is >1.5.

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HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

The tip caps of the Fluzone High-Dose prefilled syringes may contain natural rubber latex.

Fluzone High-Dose

Prefilled syringe, without needle, 0.5 mL, package of 10 prefilled syringes per carton – NDC 49281-385-65.

Storage and Handling

Store Fluzone High-Dose refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen. Do not use after the expiration date shown on the label.

PATIENT COUNSELING INFORMATION

Inform the patient or guardian that Fluzone High-Dose contains killed viruses and cannot cause influenza. Fluzone High-Dose does not prevent other respiratory infections.

- Vaccine recipients and guardians should be instructed to report any severe or unusual adverse reactions to their health care provider and/or to VAERS.

Product information as of July 2010.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

Printed in USA

MKT20500-1-1R

5959-60-61

Table 4. Enhanced-immunogenicity seasonal influenza vaccines in development for use in persons age 65 years and older

Technology	Manufacturer
Recombinant baculovirus/insect cell culture-derived, high-dose, trivalent HA	Protein Sciences
Recombinant, high-dose, trivalent, virus-like particles (VLPs)	Novavax
Recombinant flagellin-linked HA	VacInnate
Oil-in-water emulsion adjuvant + TIV	GlaxoSmithKline Vaccines
Oil-in-water adjuvant (MF-59) + TIV	Novartis Vaccines

already enrolled, with the 2010-2011 and 2011-2012 seasons to follow.

Until that study is finished and the results are known, Fluzone HD's labeling informs providers and recipients that "there have been no controlled studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose."

Other Pumped-Up Flu Vaccines in the Pipeline

Among leading flu vaccine candidates in advanced clinical development (Table 4) are a high-dose recombinant HA vaccine, a recombinant "virus-like particle" vaccine, a vaccine that fuses HA antigens to a bacterial protein called flagellin, and a pair of established flu vaccines spiked with "adjuvants" to punch up the recipient's antibody and cellular immunity to the HA antigens they contain.

Should any of these vaccines ultimately be licensed — and the ongoing Fluzone HD trial proves that it confers superior protection against lab-confirmed influenza to standard-dose TIV — it's entirely imaginable that large head-to-head trials may eventually be organized to try to resolve which high-immunogenicity vaccine confers the best protection against the flu.

High-Dose: An Appealing New Anti-Flu Option

This year, more than 30 million seniors will dutifully show up for an appointment or at a vaccination clinic and bare their arms for the annual flu shot. The reason, they'll be assured, is to help protect themselves from infection with this season's influenza virus and the potential health ravages it can cause.

If the goal of the flu vaccination exercise is to boost the odds of beating the 2010-2011 flu virus coming their way, this new Medicare-covered high-dose vaccine may be an easy choice for many seniors to make. ❖

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LUKE NOLL *is director of vaccine sales and corporate accounts at FFF Enterprises, Inc.*

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The Effects of Healthcare Reform on the Healthcare Industry

What effects can insurance companies, physicians, hospitals and the biopharmaceutical industry expect from the gradual implementation of healthcare reform law?

By Amy Scanlin, MS

Since President Obama signed the Affordable Health Care Reform Act on March 23, all Americans, but especially professionals in the healthcare industry, have been wondering: "How will this affect me?" While the specific changes to be imposed by this bill are still being hammered out, one thing is certain: Healthcare is intended to be available and accessible for every American, regardless of income and pre-existing conditions, and more than 30 million people who are currently uninsured will have access to insurance coverage.

Insurance has been the major headline topic associated with healthcare reform, but many additional items of importance are included in the bill that will help improve the quality of healthcare. Some of the expected highlights in both the near and not-too-distant future as the changes are implemented are covered in this article. For instance, how will changes to insurance coverage and reporting be impacted? How might hospital funding be altered? What compliance changes might be needed? And, what changes will occur in the biopharmaceuticals marketplace?

Effects of Reform on Insurance Coverage

A variety of insurance coverage changes are part of the Health Care Reform Act. The Office of Consumer Information and Insurance Oversight (OCIIO) under the Department of Health and Human Services (HHS) is ensuring proper implementation of the new market rules recommended by the National Association of Insurance Commissioners (NAIC), which took effect in September. These rules include medical loss ratios, quality care improvements, ensuring affordable rates and assisting with the implementation of state insurance exchanges.

In July, the government launched a new web portal (www.healthcare.gov) with insurance and participating provider information. The portal's first educational phase allows consumers to compare insurance programs, find out what is covered and locate network providers. (Those with

Medicare are referred to the existing Medicaid website.) The portal also lists information about Medicare and the Children's Health Insurance Program (CHIP), such as eligibility and a summary of available programs in each state. Information about eligibility requirements, coverage limitations and premium descriptions of state-based high-risk pools, which provide insurance to those with pre-existing conditions who are not presently insured, also is included. However, states are not required to provide high-risk pools, and in those cases, HHS will provide coverage. The next phase of web portal implementation, scheduled to take place in October, will present more detailed information about private insurance options, including cost and functionality comparisons, as well as more information about Medicaid and CHIP.

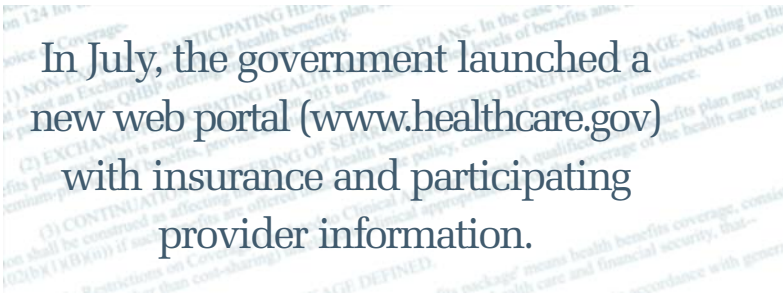
While patients are presently required to purchase either public or private insurance (or pay a penalty for not doing so), providers are not required to continue seeing existing patients or to take on new patients through the public insurance exchanges. However, there are incentives to encourage doctors to accept new Medicare patients, one of which is a 10 percent Medicare primary care and insurance bonus for underserved areas between 2011 and 2015. If their charges for nursing, home and office visits comprise at least 60 percent of total Medicare charges, family practice physicians and those specializing in pediatrics, geriatrics and internal medicine will receive a 10 percent bonus for those services between 2011-2016.[1]

A reduced Medicare payment structure, which was supposed to take place June 1, was put on hold temporarily with the signing of the Preservation of Access to Care for Medicare Beneficiaries and Pension Relief Act of 2010. This act provides a 2.2 percent increase in Medicare payments retroactive from June 1 through Nov. 30, 2010. And, Congress is continuing to work on legislation to "fix" Medicare, which is anticipated to cost about $6.5 billion.[2]

For 2010, Medicare re-established the "floor" for physician payment geographic differentials, which had expired in 2009. In 2011, the practice expense adjustment will be increased to the national average in Wyoming, Montana, North and South Dakota and Utah. According to the American Medical Association, physicians in 50 states, Puerto Rico and the Virgin Islands will benefit from this adjustment.[1]

Medicare's Physician Quality Reporting Initiative (PQRI) incentive payments have been extended through 2014. These payments will be 1 percent in 2011 and 0.5 percent from 2012 to 2014. Also, physicians who participate in a maintenance certification program will receive an additional 0.5 percent bonus. However, beginning in 2015, physicians who do not participate in the PQRI program will be penalized at a rate of 1.5 percent in 2015 and 2 percent thereafter.[1]

Medicaid primary care payment rates will be boosted to match the Medicare rates in 2013 and 2014, and the federal government will cover the entire cost of new Medicaid enrollees from 2014 to 2016. States are encouraged to provide Medicaid insurance to low-income adults who have incomes up to 133 percent below the federal poverty level, or equaling $14,400 for an individual in 2010. Also, primary care physician bonuses for those who accept both Medicare and Medicaid are anticipated, with a new care delivery model that will boost quality and efficiency while maximizing the physician workforce.[3]



There are some problems associated with the changes in Medicare and Medicaid. Critics say that just two years of Medicaid pay increases will not be sufficient to solve the problem of an influx of new patients with fewer physicians willing to care for them. Poll results were nearly evenly split when primary care physicians were asked if they would see new Medicaid patients if rates were raised to those of Medicare; however, 81 percent said they would take new Medicaid patients if the rates were raised to those of private insurance.[4]

Two other important changes due to healthcare reform are now in effect. First, a pre-existing condition insurance program (PCIP) has been established for those who have been unable to get insurance for six months or more due to a pre-existing condition. Second, self-insured group health plans are now required to provide external appeals of an independent third-party reviewer of claim denials related to medical necessity, not just internal review as was previously the case. Fully insured plans regulated by states have long been required to provide external review.

Effects of Reform on Physicians

Physicians also will be affected by healthcare reform. Definitions and methodologies for determining what constitutes clinical services, quality improvement and other non-claims costs for carrying out the medical loss ratio provision will be spelled out by the NAIC. In the meantime, the debate continues on how to translate this new law into detailed rules, and what constitutes quality care and a minimum standard of clinical services.

More concrete, however, is the expectation that physicians will see improved revenue streams and lower overhead from insurance companies. New national rules for this revenue stream are in development and will be implemented between 2013 and 2016. There also is the expectation that paperwork will be simplified.

Doctors who participate in state-based exchange-funded insurance programs also can expect closer scrutiny and greater requirements for compliance under the new healthcare reform law, as well as the False Claims Act enacted in 2009. The Health Care Reform Act requires the development and maintenance of a compliance program in order to participate in state-based exchanges, and the HHS together with its Office of Inspector General (HHS-OIG) will establish the program requirements, along with the timeline for implementation. Previously, compliance guidance provided by HHS-OIG had not been mandatory.

Doctors who participate in state-based exchange-funded insurance programs also can expect closer scrutiny and greater requirements for compliance.

Compliance requirements include written standards and procedures for the office, as well as training and monitoring programs of compliance-related issues. Those who report potential violations of the requirements can remain anonymous, and disciplinary actions must be clearly defined for violators. More information on compliance can be found at the HHS-OIG website at http://oig.hhs.gov/fraud/complianceguidance.asp. In addition, a helpful checklist and excerpt from a keynote address delivered by Daniel R. Levinson, Inspector General for the Department of Health and Human Services, at the Health Care Compliance Association's Annual Compliance Institute on April 19, can be found at http://oig.hhs.gov/testimony/docs/Qs_for_compliance_professionals.pdf.

The establishment of electronic health records (EHR) also is part of healthcare reform. The Health Information Technology for Economic and Clinical Health Act (HITECH Act) alloted nearly $80 million for the adoption and use of health information technology (HIT).[5] The "certified EHR technology" that qualifies for financial incentives must meet the criteria established by the Office of the National Coordinator for Health Information (ONC) and must be used in a "meaningful" way, as defined by the Centers for Medicare and Medicaid Services (CMS). However, many critical comments of an earlier draft said the "meaningful use" requirements were too severe and "all or nothing," which has resulted in a three-staged approach for implementation of meaningful use.

In stage I, the capturing of health information into a structured format that allows for tracking of conditions and the communication of care is required. In this stage, the establishment of functionalities that will allow for future improvements is stressed. In stage II, a more rigorous exchange of health information in the "most structured format possible," such as the use of computerized provider order entry (CPOE) and the electronic transmission of diagnostic testing results are required. More rigorous electronic prescribing and laboratory testing are expected. Stage III will focus on quality improvements of the systems. CMS admits in its final ruling that the requirements for meaningful use are "ambitious" with the current state of technology and standards of care, but it anticipates that the evolution of improvements will keep pace.[6]

Incentives to providers for a Medicare fee-for-service program who demonstrate the use of certified EHRs in a meaningful way will be paid out beginning in 2011. Those who have not demonstrated a meaningful use of certified EHR technology by 2015 will receive only 99 percent of their fees for professional services. And, the percentage will be reduced by 1 percent each year thereafter that meaningful use is not demonstrated. Similar incentives and penalties also will be imposed on hospitals that do not demonstrate meaningful use.

Providers receiving Medicaid payments must demonstrate meaningful use by 2016 in order to receive any incentive payments in 2017, and they also must meet the criteria each year after 2016 to continue eligibility to receive incentive payments. The same is true for Medicaid-eligible hospitals. Participation in a Medicare Fee-for-Service and Medicaid Advantage programs cannot receive duplicate incentives where meaningful use of EHRs are concerned. However, should a provider leave one practice for another, they can continue to receive payments as long as they maintain meaningful use of a certified EHR.

Effects of Reform on Hospitals

Because there is concern that doctor-owned hospitals may choose healthier patients over unhealthy ones, the new law prohibits new physician-owned hospitals from participating in Medicare and it limits the expansions of existing doctor-owned hospitals. The goal is to prevent any suggestion of impropriety or conflict of interest. According to the American Medical Association's David Glendinning, "Advocates of the hospitals say the provision is a poison pill for their industry and will decrease patients' options for

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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
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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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specialized, high-quality care."[3]

Another new change amends the "in-office ancillary service" exception to the federal Stark Law, which governs physician self-referral for Medicare and Medicaid patients. This amendment requires physician-owned hospitals that refer patients for MRI, CT and PET services within the doctor's group to provide a list of alternative provider locations in the area as well.[7]

While 41 states require hospitals to report their charges publicly, three separate pieces of legislation promoting transparency propose that hospitals and physicians disclose their prices.

Yet another change involves pricing. While 41 states require hospitals to report their charges publicly, three separate pieces of legislation promoting transparency propose that hospitals and physicians disclose their prices, and one piece of legislation even proposes the disclosure of wholesale and retail prices for services and products. Because some states already require prescription drug information be public, if this legislation is approved, insurance providers also will be required to list all payments and copays (some companies already do this for common procedures).

However, critics argue that price and quality cannot be separated. That being said, without a good measurement of quality in healthcare, it is difficult for patients to differentiate services and providers. The real key to transparency, critics argue, is linking quality and fees. The CMS already posts Medicare rates and quality information for 35 procedures.[8]

Effects of Reform on Biopharmaceuticals

Many individual market insurance plans previously did not offer pharmaceutical coverage. However, the essential benefits package in the new healthcare plan stipulates that all fully insured plans must include pharmaceutical coverage. Yet, there does not appear to be any special insurance provisions for patients who rely on high-cost plasma medications, because all carriers will be required to accept these individuals, spreading their risk over the broader population. If these treatments are included in the essential benefits package, then all policyholders would have access to coverage of these treatments.

The healthcare reform law did give a boost to small biomedical firms with the congressional approval of the Therapeutic Discovery Tax Credit. This tax credit awards firms in support of new research and the creation of new therapies that target unmet medical needs, while advancing the goal of curing cancer and creating greater competitiveness for the U.S. in the international biomedical marketplace. The credit is worth up to $5 billion per firm, or up to 50 percent of the qualifying investment. Companies that are awarded the tax credit also may choose to receive a grant in lieu of the tax credit. The application period ended July 21 and the announcement of firms awarded the credit are expected to be announced in October.

Navigating Healthcare Reform

Healthcare reform will continue to be an evolving topic as policies and procedures are determined and the deadline for requirements fall into place. Through diligence in planning and preparation for the necessary changes, those in the healthcare industry will be better able to navigate the changing healthcare requirements. ❖

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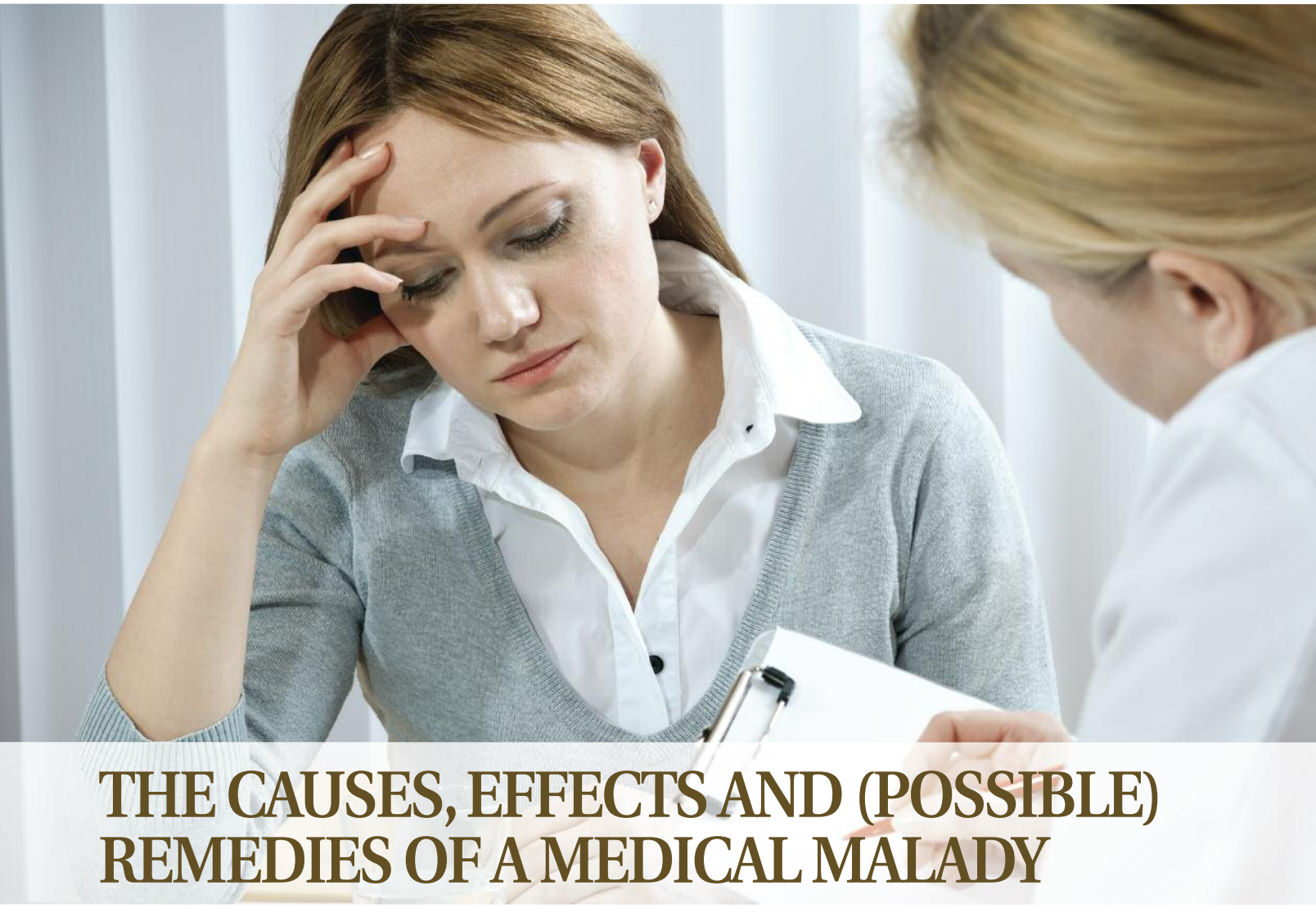

THE CAUSES, EFFECTS AND (POSSIBLE) REMEDIES OF A MEDICAL MALADY

While there has been virtually no decrease in the number of medical misdiagnoses in the U.S., awareness of the problem is growing, resulting in increased recommendations for reducing the incidence rate.

By Ronale Tucker Rhodes, MS

By the time Jennifer Rufer discovered that she had been misdiagnosed at age 22 with a rare form of cancer, it was too late. She had already needlessly suffered through three years of chemotherapy and surgeries, including a hysterectomy that left her unable to live the life she imagined as a mother. It all started when she began having irregular menstrual bleeding and was given a routine pregnancy test that came back positive. The problem: While she was producing high levels of human chorionic gonadotropin (HCG), which happens when a woman is pregnant, there was no fetus —

which is sometimes a sign of a rare form of cancer, a gestational trophoblastic tumor. Yet, although specialists were unable to find a tumor, she was diagnosed with cancer and immediately started on chemotherapy. But, after months of debilitating treatments, repeated pregnancy tests (using the same lab test) continued to show her HCG levels at between 250 and 350, compared to a normal level of about five. The next step was a hysterectomy, followed by additional surgeries, from which tissue samples showed no evidence of cancer. The stunning revelation: She never had cancer to begin with. The pregnancy test was giving a false positive result.

A jury ruled that the hospital that treated Rufer and the maker of the pregnancy test were both at fault, and unanimously awarded Rufer $15 million for pain and suffering and $452,000 more for economic damages, including lost wages and the costs of having children using a surrogate mother. But, this in no way makes up for what she endured due to misdiagnosis — one of many types of misdiagnoses that occur far too often. Discovering why misdiagnoses happen and what can be done to reverse their trend, which shows no sign of decreasing, is more important than ever.

Defining Misdiagnosis

There are three major categories of medical misdiagnosis. A false positive is a misdiagnosis of a disease that is not actually present. A false negative is a failure to diagnose a disease that is present. And, equivocal results are an inconclusive interpretation without a definite diagnosis.[1]

Misdiagnosis occurs in many ways. For instance, it can occur due to failure to properly diagnose an underlying condition, the cause of a health condition, the subtype of a properly diagnosed disease such as diabetes or heart disease, a condition related to the original disease, or any complications that the original disease caused. It also can result when there is a diagnosis of the wrong disease, a diagnosis of an illness when the patient is actually healthy, or when the diagnosis is missed or delayed.[2]

No Rare Occurrence

According to an analysis of autopsy data, the five most commonly misdiagnosed diseases (based on relative incidence) are pulmonary emboli, myocardial infarctions, aortic aneurysms, neoplasms and cardiovascular disease. And, in an analysis of malpractice data, the five most commonly misdiagnosed diseases were breast cancer, colorectal cancer, infections, skin cancer and fractures.[3]

With all of the diagnostic tools available to modern medicine, misdiagnosis should be a rare occurrence. But, it's not.

With all of the diagnostic tools available to modern medicine, misdiagnosis should be a rare occurrence. But, it's not. Studies of autopsies have shown that doctors seriously misdiagnose fatal illnesses 20 percent of the time, resulting in millions of patients being treated for the wrong disease.[4] For instance, in a study of autopsies published in the *Mayo Clinic Proceedings* comparing clinical diagnoses with postmortem diagnoses for medical intensive care unit patients, in 26 percent of cases, a diagnosis was missed clinically. If the true diagnosis had been known prior to death, it might have resulted in a change in treatment and prolonged survival in most of these misdiagnosed cases.[3]

Medical imaging is another area where rates of misdiagnosis are high. Radiology-specific studies have shown significant error rates, with the failure to detect abnormalities in 25 percent to 32 percent of cases where disease was present (false negative) and incorrectly diagnosing diseases in 1.6 percent to 2 percent of cases that were actually normal (false positive).[3]

Misinterpretation and difficult-case disagreement rates also are higher for more advanced modalities. In one study, substantial disagreement between radiologists when using MRI for diagnosis in patients suspected of lumbar disc herniations was present in 30 of 59 patients (51 percent).[3]

While this is just a sampling of the astonishing rates of medical misdiagnosis, the more astonishing fact is that the rate has not really changed since the 1930s.

Error, Oversight or Apathy?

Why does misdiagnosis occur? The most common causes of misdiagnosis are a diagnostic "blind spot," such as a conscious decision not to pursue a clinical finding, failure to account for a symptom or sign, atypical presentations and/or inadequate follow-up of abnormal laboratory findings. In addition, the most common factors leading to medical errors include failure to obtain a proper medical history, order the appropriate diagnostic tests or provide adequate follow-up. In about 40 percent of most malpractice cases, the physician failed to issue a proper follow-up plan, perform an adequate physical examination or interpret a diagnostic test correctly. What's especially interesting is that about three-quarters of cases are due to failures in judgment, half are due to lack of vigilance or memory and only one-quarter are due to negligence itself.[3]

Other reasons for misdiagnosis include failing to pay attention or respond to a patient's complaints or symptoms, failure to refer a patient to a specialist in a timely manner and familiarity with only the most common of the approximately 20,000 human diseases.[2] While most patients trust that their physician has enough skill and knowledge to locate their health problem and take the necessary steps to fix it, most doctors are not familiar with every health condition that exists. It's simply not possible to know how to treat every infection and disease under the sun. Plus, some conditions are rare and less likely to occur in patients, and some medical conditions have similar symptoms.[5]

The most common factors leading to medical errors include failure to obtain a proper medical history, order the appropriate diagnostic tests or provide adequate follow-up.

A final reason for misdiagnosis could be that "under the current medical system, doctors, nurses, lab technicians and hospital executives are not actually paid to come up with the right diagnosis. They are paid to perform tests and to do surgery and to dispense drugs."[3] Therefore, healthcare professionals may have the best of intentions, but they have little economic incentive to spend time double-checking their instincts, and hospitals have little incentive, other than that threat of malpractice suits, to give them the tools to do so.

Effects of Misdiagnosis

Misdiagnosis can cause major problems for patients, healthcare professionals and organizations, and insurance providers.

For patients, quality of care is a big issue. Getting a false positive diagnosis, such as in Rufer's case, can result in unnecessary treatments and even surgery before discovering they don't have the diagnosed disease. With a false negative diagnosis, the undetected illness can cause the patient's condition to deteriorate to the point where more extensive intervention becomes necessary with the increased risk of a poor outcome.[1] And a delayed diagnosis can result in no treatment at all.

Joanne Pease understands the consequences of a delayed diagnosis very well. When Pease's first-born son, Curtis, was given live vaccines, he contracted the measles. Because physicians failed to test him for immune deficiency, it was unknown why he had contracted the disease from the vaccine. And, when her second son, Jeff, was born, Pease had concerns that the same thing could happen. The doctors, however, told her it wasn't likely and recommended Jeff be vaccinated. After the second dose of polio vaccine, Jeff got very sick. He tested positive for polio, and then both sons were diagnosed with X-linked agammaglobulinemia (XLA), a primary immune deficiency. Jeff was left with a poorly functioning and very short leg requiring years of painful surgeries and therapies. Had Curtis been tested and diagnosed in infancy,

Jeff would have been as well, sparing him from life-long impairment.

Anxiety and distress in patients also can be amplified with misdiagnosis. They may worry when an illness is not improving despite treatment, or when a disease progresses to a serious stage because necessary care was delayed. Patients also are concerned about lost income and mounting costs for prolonged treatments or repeated testing as a result of diagnostic errors or equivocal interpretations.[1]

In 2004, a total of $4.2 billion was paid in medical malpractice lawsuits, with the highest payments (and the most common type of lawsuits) related to misdiagnosis, failure to diagnose or delayed diagnosis.

Physicians often share patients' anxiety in such cases. Most physicians have the utmost concern for their patients; they uphold the medical creed to "first, do no harm." But, the rate of misdiagnoses has caused concern among many patients, and this reflects not only on physicians' confidence to correctly diagnose, but their ability to reassure their patients that their diagnoses are correct. In fact, a YouGov survey commissioned in 2005 by The Isabel Medical Charity revealed that 60 percent of people fear illnesses will not be correctly diagnosed when they visit their general practitioner. A third of the respondents had directly experienced or knew someone who had experienced a medical error, with 57 percent of the mistakes due to misdiagnosis.[6]

In 2004, a total of $4.2 billion was paid in medical malpractice lawsuits, with the highest payments (and the most common type of lawsuits) related to misdiagnosis, failure to diagnose or delayed diagnosis.[3] Aside from lawsuits, insurance companies often are faced with higher payouts to healthcare organizations due to misdiagnosis. For instance, if patients fail to get the treatment they need, resulting in more severe illness, the costs will be even greater. In one typical case, a patient who was not properly diagnosed with a primary immune deficiency, which required treatment with intravenous immune globulin (IVIG), ended up in the hospital with a severe case of pneumonia, which ultimately cost the insurance company an additional $75,000, on top of the cost of IVIG treatments she eventually received.

Curbing the Persistent Problem

With almost no change in the rate of misdiagnoses over the years, what can be done to curb this persistent problem? For one, the need for a proper history and physical should be stressed. And policies, procedures and systems that can reduce the most common errors that lead to misdiagnosis should be instituted.[3]

One such system could be a pay-for-performance program to give physicians more economic incentive to decrease the number of misdiagnoses. Such a system was developed by Mark B. McClellan, MD, PhD, administrator for the Centers for Medicare and Medicaid Services, and is supported by the Isabel Medical Charity. The software, called Isabel, allows doctors to type in a patient's symptoms and, in response, gives a list of possible causes. It is in use by Medicare, and a few insurers are also experimenting with it. And, while it doesn't replace doctors, it does make sure they consider some unobvious possibilities that they may not have seen since medical school.[4] Some U.S. physicians have been quick to reap the benefits from the Isabel system, and five top children's hospitals in the U.S. have already adopted the pediatric version.[6] Yet many have not adopted the system, perhaps because of its cost, which is $80,000 a year for a typical hospital and $750 a year for an individual doctor. But, then, misdiagnosis costs far more.

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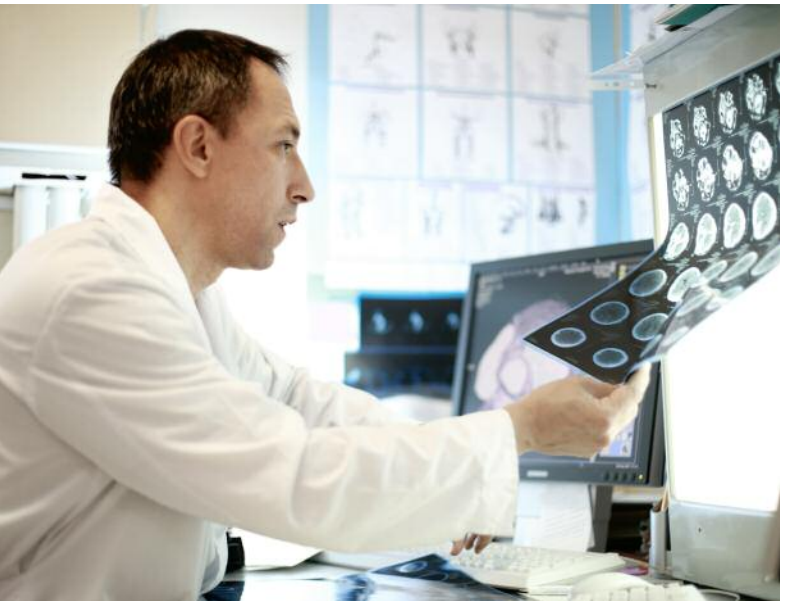

Familiarization with the commonly misdiagnosed conditions and the factors that lead to misdiagnosis also would help greatly. This could include continuing medical education courses that educate physicians about the critical breakdown points leading to misdiagnosis. Primary care physicians, in particular, would benefit from this type of education since they are usually the first physician that the patient presents to with their symptoms.[3]

One of the reasons that the rate of misdiagnoses has yet to decrease could be a lack of attention from the public.

Familiarity with specific disease diagnoses and more frequent referrals to specialists also would help. Extensive research has demonstrated the relationship between case volume and patient outcome for a variety of medical conditions and procedures. Case volume refers to the number of specific types of diagnoses handled by a particular physician or healthcare organization (i.e., their familiarity with the disease diagnosis). One review of 128 studies examined 40 conditions or procedures, and found a statistically significant relationship between higher case volumes and better clinical outlines in 80 percent of those cases.[1]

Another study examined the mammographic interpretation sensitivity demonstrated by individual radiologists. High sensitivity indicated the detection of a high percentage of true positive breast cancer cases. Radiologists who read more than 300 mammograms per month detected an average of 78.6 percent of cancers, compared with 71.5 percent found by radiologists who read 100 or fewer per month. In essence, the higher-volume, more experienced radiologists were more likely to detect a cancer with the mammogram.[1]

The Need for Greater Attention

Joseph Britto, a former intensive-care doctor, compares medicine's attitude toward mistakes with the approach the aviation industry takes. According to Britto, at the insistence of pilots who have the ultimate incentive not to mess up, airlines have studied their errors and nearly eliminated crashes. "Unlike pilots," he says, "doctors don't go down with their planes."[4]

One of the reasons that the rate of misdiagnoses has yet to decrease could be a lack of attention from the public. The United States healthcare system has lagged behind most other industries regarding the attention paid to ensuring safety, and the comparison with the airline industry is a good one. For example, the aviation industry has focused on producing a safety system since the 1940s, with more public attention centered on improving safety in the aviation industry than on healthcare — despite the higher risk of injury or death as a result of medical error versus being involved in an airplane crash. Media coverage seems to have been a major factor that encouraged safety improvements within the aviation industry.[1] Could that be the answer for the healthcare industry, too? ❖

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

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Myths and Facts: Pertussis

An epidemic of pertussis in California — of a size not seen in some 50 years — makes educating the public about this disease and how to prevent it more important than ever.

By Ronale Tucker Rhodes, MS

In August, as kids were returning to school, educational districts throughout California sent health alerts to school administrators and parents about the growing rate of pertussis cases being reported in the state, and the front pages of local newspapers warned of a pertussis epidemic. As of Aug. 10, 2,774 cases of pertussis, also known as whooping cough, were reported to the California Department of Public Health (CDPH) — a sevenfold increase from the 395 cases reported through the same date in 2009. Of these reported cases, 159 (12 percent) had been hospitalized, the majority of whom were infants younger than 6 months old, and seven infants younger than 2 months old had died — none of whom had received any doses of pertussis-containing vaccine. And, the CDPH projected that if current trends continue, California will likely see more cases of pertussis than it has in more than 50 years and the highest rate of the disease in 47 years.[1]

Yet, while California is the only state as of this writing to report an epidemic of pertussis, reporting of the disease can be spotty or delayed, according to Jeff Dimond, a spokesman for the Centers for Disease Control and Prevention (CDC).[2] And, with the peak season for pertussis starting in the summer, without intervention, the number of cases could potentially get much larger.

Lack of information is often the culprit behind the spread of this potentially dangerous disease. So, to avoid a future epidemic of this level, there is a serious need to distinguish between the myths and facts about what causes pertussis, how to treat it and, ultimately, how to prevent it.

Separating Myth from Fact

Myth: Pertussis is no longer common now that there is a vaccine to prevent it.

Fact: Pertussis was a leading cause of childhood illness and death in the U.S. in the first half of the 20th century. But, after the introduction of a vaccine, the number of cases reached a low in the mid-1970s. Since then, the incidence of pertussis has been increasing primarily among children too young to have completed the full course of vaccinations in teenagers, and in adults whose immunity has faded.[3]

In fact, periodic outbreaks of pertussis are not uncommon. The disease is endemic worldwide, and some 5,000 to 7,000 cases are reported in the U.S. in a normal year, according to the CDC. Epidemics occur every three to five years in the U.S., with the most recent in 2005, when there were more than 25,000 reported cases nationwide, and nearly 3,200 in California, where seven people died.[2] In countries where children aren't routinely vaccinated, pertussis sickens 51 million and kills 600,000 people annually.[4]

Myth: Pertussis affects only children.

Fact: Pertussis affects people of any age. The disease was most common in infants and young children before vaccines were widely available. But, now that most children are immunized before entering school, the higher percentage of cases is seen among adolescents and adults.[5] This is because the vaccine children receive eventually wears off, leaving most teenagers and adults susceptible to the infection during an outbreak. Still, children are a high-risk population for infection. Because they aren't fully immune to pertussis until they've received at least three shots, those 6 months and younger are at greatest risk of contracting the infection.[6]

In the current epidemic occurring in California, however, there is a high incidence of pertussis in Hispanic infants (all of the fatalities have been Hispanic). According to Dr. Gilberto Chavez, deputy director of the CDPH's Center for Infectious Disease, lack of information and inoculations in agricultural regions in the state's Central Valley, home to many Latino farmworkers, might be a culprit in the high incidence in this area.[2] In fact, cities in the Central Valley have the highest number of reported cases of pertussis.[1]

Pertussis is a serious disease that can cause permanent disability in infants and even death.

Myth: Pertussis is an influenza-like viral infection.

Fact: Pertussis is not a viral infection; it is an upper-respiratory infection caused by the Bordetella pertussis or Bordetella parapertussis bacteria. It is easily spread from person to person, which happens when an infected person sneezes or coughs and tiny droplets containing the bacteria move through the air and are breathed into the lungs of anyone who happens to be in the vicinity. The bacteria then multiply in the airways and produce toxins that interfere with the respiratory tract's ability to get rid of the germs, causing the development of thick mucus, as well as inflammation that narrows breathing tubes in the lungs.[7]

Myth: Pertussis is not a dangerous disease.

Fact: Pertussis is a serious disease that can cause permanent disability in infants and even death. Symptoms usually develop about a week after exposure to the bacteria, and severe coughing episodes start about 10 to 12 days later. In children, the coughing often ends with a "whoop" noise, caused when they try to take a breath after a coughing fit. However, the whoop noise is rare in patients under 6 months of age and in adults.[5]

Coughing spells, which can last from one to two minutes and often result in vomiting, severe facial congestions and a feeling or appearance of suffocation, happen as little as twice a day or as many as 50 a day. Between coughing attacks, the sufferer appears and usually feels perfectly well.[8]

Other pertussis symptoms include runny nose, slight fever (102 degrees Fahrenheit or lower) and diarrhea. While the outlook is generally very good in older children and adults, infants are at highest risk of death. Possible complications include pneumonia, convulsions, seizure disorders (permanent), nosebleeds, ear infections, brain damage from lack of oxygen, bleeding in the brain (cerebral hemorrhage), mental retardation, slowed or stopped breathing (apnea) or death.[5]

Myth: Doctors can easily diagnose whooping cough.

Fact: Because the symptoms of pertussis often mimic those of a cold, flu or bronchitis, many cases go undiagnosed. In addition, there is great variation in the severity and duration of the illness. Therefore, a key to clinical diagnosis is attacks of choking cough separated by long intervals of no coughing at all. Plus, diagnosis is often made only if the physician hears the cough. The website www.whoopingcough.net provides sound clips of children and adults with pertussis.[8]

When a diagnosis can't be made by asking about symptoms or listening to the cough, medical tests may be needed to confirm the disease. These include a nose or throat culture and test, blood tests to check for high white blood cell counts, and a chest X-ray to check for the presence of inflammation or fluid in the lungs.[9]

Myth: Pertussis resolves in five to 10 days.

Fact: The initial stage of pertussis itself, when cold-like symptoms present, lasts between one and two weeks. The paroxysmal stage that follows with severe coughing spells lasts another two to four weeks. And, the convalescent stage of the disease, which is less severe, typically lasts between three and four weeks, but it can continue for months.[4] In China, pertussis is known as the 100-day cough.

Myth: The pertussis vaccine does not adequately protect people from contracting the disease.

Fact: The pertussis vaccine is the best prevention against the disease if given as scheduled. It is often given in combination with vaccines against two other serious diseases, diphtheria and tetanus, and is known as the DTaP vaccine. Children should receive a series of five DTaP vaccines at ages 2 months, 4 months, 6 months, 15 to 18 months and 4 to 6 years. In addition, a booster shot, known as the Tdap vaccine, should be given to children at age 11 or 12 and then to all individuals every 10 years after that. Some healthcare organizations strongly recommend that adults up to the age of 65 receive the adult form of the vaccine against pertussis. Vaccine side effects may include fever, crankiness or soreness at the site of the injection. And, in rare cases, severe side effects can include persistent crying lasting more than three hours, high fever, and seizures, shock or coma.[5,10]

In the case of a pertussis outbreak, children under age 7 who have not been immunized should not attend school or public gatherings, and should be isolated from anyone known or suspected to be infected for at least 14 days after the last reported case.[4]

Myth: Antibiotics are the treatment of choice for whooping cough at any stage in the disease.

Fact: In the initial stage of the disease, antibiotics are most effective in treating pertussis. However, most individuals are not diagnosed until the cough starts in the second stage of the disease, when antibiotics are less effective.[4] Even so, antibiotics at this stage still can help reduce an infected individual's ability to spread the disease to others.[5] Family members not yet infected also can be given preventive antibiotics.[11]

Over-the-counter medications have little effect on whooping cough and are discouraged. What can help are fluids given through the vein if coughing spells are severe enough to prevent the person from drinking enough, and sedatives may be prescribed to young children. Infants younger than 18 months need constant supervision because their breathing may temporarily stop during coughing spells, and those with severe cases of pertussis should be hospitalized.[5]

Some lifestyle and home remedies also may be helpful for those dealing with coughing spells, including getting plenty of rest, drinking plenty of fluids, eating smaller meals (to avoid vomiting after coughing), vaporizing the room (to help soothe irritated lungs and loosen respiratory secretions), cleaning the air (to rid it of irritants that can cause coughing) and preventing transmission by covering a cough and washing hands often.[12]

Myth: The pertussis vaccine causes dangerous adverse reactions.

Fact: The first whole-cell pertussis vaccine, developed in the 1930s and in widespread use by the mid-1940s, was linked to some serious side effects. However, the whole-cell pertussis vaccine is no longer available. Today, the combined DTaP vaccine, licensed in 1991, is a more purified "acellular" version and produces fewer side effects. Getting pertussis, diphtheria or tetanus poses much more risk than getting the vaccine.[13,14]

The risk of the DTaP vaccine causing serious harm or death is extremely small.[14] Most children have no serious reactions from this combined vaccine. But, about 20 percent to 40 percent of children have some local reaction, such as pain, redness or swelling after the first three doses of DTaP, and after the fourth and/or fifth doses, these local reactions are more frequent. A temperature of 101 degrees Fahrenheit occurs in only 3 percent to 5 percent of children. More serious reactions, such as persistent crying, higher fever and febrile seizure, are rare and occur in fewer than one in 10,000 doses.[13]

There are some people who should not receive either the DTaP or Tdap vaccine, including those who have had a serious allergic reaction to a previous dose of either vaccine, or who have developed encephalopathy (brain injury) not due to another identifiable cause. In addition, someone with a recognized, possible or potential neurologic condition should delay receiving either vaccine until the condition is evaluated, treated and/or stabilized. While the vaccine does not cause neurological disorders, it can cause an already present underlying condition to show itself.[13]

Getting pertussis, diphtheria or tetanus poses much more risk than getting the vaccine.

Dispelling the Myths Now

With seven deaths in California caused by pertussis, the seriousness of preventing the disease can't be overstated. While the pertussis vaccination is the most effective way to prevent the disease, history has shown that epidemics continue to occur. So, understanding what this disease is, its symptoms and how to treat them are just as important. ❖

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(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 Inmunol 2007;27:628-633.

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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.**

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GRIFOLS

Immune Globulin Intravenous (Human)
Flebogamma® 5% DIF
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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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IVIG and Alzheimer's Disease: Could It Work Where Everything Else Has Failed?

"God gave us memory so that we might have roses in December."
— JM Barrie

By KEITH BERMAN, MPH, MBA

THE DREADED PROSPECT of an Alzheimer's disease diagnosis is more feared than cancer by many. Alzheimer's slowly robs its victims of everything: the ability to think abstractly and solve problems, perform familiar tasks, remember names and events and have conversations. Unique personality traits eventually disappear, which are often replaced by anxiety, depressive symptoms or inappropriate behaviors. In the end, most sufferers are unable to recognize familiar surroundings or close family members.

This isn't a normal part of aging. Alzheimer's is an insidious degenerative disease that incapacitates or kills billions of neurons as it literally shrinks its victims' brains. At autopsy, one finds more telltale detritus: hard insoluble plaques made of a protein called beta amyloid (Abeta) and twisted masses of a normal structural nerve cell protein called "tao" that form what pathologists describe as neurofibrillary tangles.

More than five million people in this country have Alzheimer's disease, including one in eight persons aged 65 and older.[1] With the leading edge of the baby boom generation set to double the over-65 population during the next 20 years, Alzheimer's has long been a leading target for development of potentially disease-modifying drugs.

Drug Candidates Keep Falling Short

But up to now, the pharmaceutical industry has managed to produce only a large and costly graveyard of failed Alzheimer's drug candidates. Throughout

just the last decade, more than 20 investigational agents that reached Phase III trials were shown to be ineffective; a few were actually harmful.

Some of these drugs were intended to address known aspects of Alzheimer's-related damage, such as oxidative damage, inflammation or mitochondrial dysfunction. Some have been designed to clear existing amyloid plaques, prevent Abeta formation or deposition, or disassemble neurofibrillary tangles.

In each case, hopes have been pinned to a narrowly defined theory of Alzheimer's pathophysiology that neatly dovetails with the mechanism of action of the drug candidate. For example, Pfizer recently decided to investigate an antihistamine called Dimebon, which acts to help stabilize cellular mitochondria and showed seemingly promising results in a Russian Phase II trial. Severe mitochondrial dysfunction is well-documented in Alzheimer's brain cells. The drug failed to work in a large Phase III trial.

What Causes Alzheimer's: New Theories, Opportunities, Questions

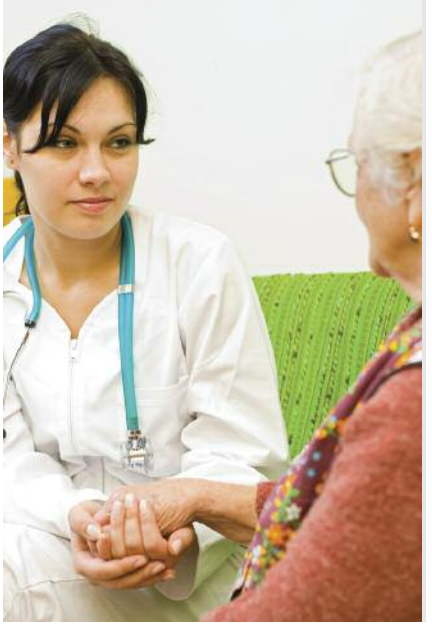
Exactly what goes wrong to begin with in Alzheimer's disease remains a mystery that lengthens the odds of finding an effective drug. But more and more evidence points to single Abeta 42 peptide "monomers" linking together into highly toxic "oligomers" that disrupt nerve synapses and various nerve cell functions. People with Alzheimer's seem to produce much less of the antibody that normally binds and clears these neurotoxic oligomers before they can do their damage. Lots of other mayhem is going on as well, including damaging chronic inflammatory activity and those changes to tao protein that disable axonal transport and create the hallmark tangles.

These days, the "beta amyloid theory" to explain Alzheimer's has the most adherents and is the leading focus of Alzheimer's drug research and development activity. A recent landmark study has at last discovered a "signature" profile of Abeta 42 peptide and a pair of tao proteins in the cerebrospinal fluid (CSF) of persons with mild cognitive impairment. With results from a simple spinal tap, physicians may soon be able to predict with nearly 100 percent accuracy who will advance to clinical Alzheimer's disease.[2] The implications are obvious: An early lab test-based diagnosis creates an opportunity to intervene with a therapeutic to delay or potentially even halt the disease process years before it progresses to full-blown dementia. Now all we need is that effective drug.

Alzheimer's is an insidious degenerative disease that incapacitates or kills billions of neurons as it literally shrinks its victims' brains.

Earlier, the Canadian firm Neurochem touted the prospects of a small molecule dubbed Alzhemed that crosses the blood-brain barrier, binds to soluble Abeta monomers and appears to interfere with formation of amyloid plaques. In a randomized pivotal trial involving more than 1,000 Alzheimer's patients, Alzhemed had no discernible effect on cognitive decline.

The list of dead and moribund Alzheimer's drug candidates is long and keeps getting longer.



Meanwhile, new unanswered questions continue to challenge Alzheimer's researchers. Why do CSF Abeta levels first increase in the years before a clinical diagnosis is made, and then decline? What's the normal functional role of Abeta in the first place? Are Abeta monomers actually neuroprotective as some recent research suggests?[3] What do we make of new evidence that Abeta is an important antimicrobial peptide in the brain?[4] Why do certain investigational anti-Abeta vaccines and monoclonal antibodies clear Abeta in some subjects, while causing inflammatory arthritis and brain swelling in others?

Given all we don't know about why people do or do not develop Alzheimer's, the notion that a single agent with narrowly directed activity can effectively slow this complex disease might be bordering on wishful thinking.

Alzheimer's, Immunology and IVIG

What, then, about all the interest in intravenous immunoglobulin (IVIG) for Alzheimer's disease? Let's step back and consider a few background points relating to the aging immune system,

Alzheimer's and experimental immunotherapy with human IVIG:

• Our ability to generate antibodies to defend against infectious or toxic threats and effectively regulate cellular immunity begins a long decline that starts around age 65 and accelerates in our 70s and 80s.

• Most Alzheimer's cases occur after age 65; the incidence of the disease climbs sharply as people reach their late 70s and 80s.

The list of dead and moribund Alzheimer's drug candidates is long and keeps getting longer.

• Levels of natural CSF and plasma antibodies directed against Abeta (including Abeta oligomers) are significantly lower in patients with Alzheimer's compared with healthy individuals.[5]

• IVIG administration lowers CSF Abeta levels in Alzheimer's patients, implying that infused anti-Abeta antibodies are binding Abeta peptide and facilitating its clearance. An in vitro model has demonstrated that IVIG facilitates microglial phagocytosis of Abeta peptide.[6]

• Anti-Abeta human antibodies in IVIG have been shown to prevent Abeta oligomer-induced neurotoxicity in an in vitro neuroblastoma cell model.[7]

• Recent evidence implicates inflammation secondary to nerve cell death and dysfunction as a distinct harmful component of the Alzheimer's disease process.[8,9] While incompletely understood, potent anti-inflammatory and other immunoregulatory functions of IVIG have been widely cited to explain its established efficacy both in certain autoimmune inflammatory neuropathies[10,11] and in an experimental model of ischemic stroke.[12]

• Findings from several early-stage human trials of IVIG,[13,14,15] as well as retrospective analyses of older adults without Alzheimer's or other dementias,[16,17] offer very encouraging early signals that IVIG may slow or delay cognitive decline.

Consider that the risk of developing Alzheimer's disease doubles every five years after age 65. While heredity clearly plays a role and certain lifestyle factors might have some influence on disease risk, there is no known underlying "cause" for most cases of Alzheimer's other than getting older.

Should IVIG ultimately prove effective in slowing progression of this disease, the fundamental therapeutic principle is straightforward: IVIG is restoring some array of critical protective antibodies that the senescent immune system can no longer make enough of on its own. We may never understand what those antibodies are or precisely how IVIG works, but that won't be anything new. No one really knows, for example, how IVIG works in chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, Kawasaki disease or mucocutaneous blistering diseases. But this ignorance doesn't seem to bother neurologists, rheumatologists and other specialists who prescribe IVIG products every day.

Several trials being planned or now in progress should soon reveal whether IVIG modifies the course of mild to moderate Alzheimer's disease or joins the graveyard of once-promising drug candidates.

IVIG: Random Book or Kitchen Sink?

Understandably, there are IVIG skeptics. Dr. Lawrence Honig, a Columbia University researcher evaluating Pfizer's humanized anti-Abeta monoclonal antibody called bapineuzumab, suggested a few years ago that trying IVIG to treat Alzheimer's disease is "like picking a random book off the shelf and hoping it's the one you want to read." His center and several hundred other clinical study sites are currently evaluating bapineuzumab in Phase III trials. "This more targeted approach makes a lot more sense," he said in an interview with WebMD.[18]

Dr. Norman Relkin at Weill Cornell Medical College, who is the lead investigator for current Phase III trials of Baxter's IVIG product, offers a decidedly different homespun perspective on the rationale for testing IVIG. "It is a kind of 'kitchen sink' approach to immunotherapy [that] throws all the antibodies in the human repertoire at the patient, hoping that those which target the amyloid pathology and those which exert an immunomodulatory effect will be of benefit," he said in a recent interview.[19]

I'm not a scientist, but honestly, a monoclonal antibody like bapineuzumab that zeroes in on a single target on the N-terminal end of an Abeta peptide seems the better fit for Honig's "random book off the shelf" analogy. On the other hand, Relkin's "kitchen sink" metaphor about IVIG works pretty well for me. After all, IVIG is essentially a concentrate of half of the circulating human immune system. Each vial contains a myriad of natural, fully functional human antibodies collected from healthy adult donors.

Now that's something worth thinking about. ❖

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KEITH BERMAN, *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Berman previously worked in product development, reimbursement development and market research roles at Baxter Healthcare, Siemens Medical and MiniMed Technologies (now a Medtronic division). Since 1989, he has also served as editor of* International Blood/Plasma News, *a blood products industry newsletter.*

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

INDICATIONS AND USAGE

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

DOSAGE FORMS AND STRENGTHS

- Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:
  - o 450 IU VWF:RCo and 450 IU FVIII activities in 5 mL
  - o 900 IU VWF:RCo and 900 IU FVIII activities in 10 mL

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- None known.

USE IN SPECIFIC POPULATIONS

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

DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution

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

Dosage in von Willebrand Disease

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

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

Dosing Schedule

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

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

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

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

Treatment guidelines apply to all VWD types

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

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

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

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

HOW SUPPLIED/STORAGE AND HANDLING

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

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

Shelf life

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

PATIENT COUNSELING INFORMATION

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

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The Octapharma family represents one of the world's leading plasma product manufacturers and we are committed to the patients we serve and to successfully bringing the products they need to market. It is our goal to provide patients with the therapy they need, when they need it. We foster a climate of innovative thinking and technology and we are dedicated to the highest standards for quality and safety set by physicians, regulatory authorities and most importantly you.

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Octapharma's worldwide commitment to coagulation disorders dates back to Octapharma Group's formation over 25 years ago. We have been providing state-of-the-art, life saving therapies around the globe and are very excited to have the opportunity to now offer these products to the US market. Our commitment to you is that we will relentlessly continue to search for new therapies and improvements in current therapies based upon your needs and those of the medical community.

Our Product
wilate® represents a new von Willebrand Factor/Coagulation Factor VIII Complex developed specifically for the treatment of von Willebrand disease patients.

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

For further information, please contact

Medical Affairs / 888-429-4535
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Turning Challenges into Opportunities

"Leadership is the art of getting someone else to do something you want done because he wants to do it."

— Dwight D. Eisenhower

By Trudie Mitschang

HEALTHCARE REFORM IS one of those hot-button topics best avoided at office water coolers and company dinner parties. But within the confines of the Premier healthcare alliance, it's far more than a politically charged headline or topic for debate; it's a driving force behind various initiatives that have become industry recognized models for reducing healthcare costs and raising standards of care.

Adept at turning challenges into opportunities, Mike Alkire, president of Premier Purchasing Partners Inc., believes one of the goals of healthcare reform must be to demolish the barriers that exist between clinicians, hospital staff, providers and payers. As the purchasing division of Premier, a healthcare performance improvement alliance of 2,400 not-for-profit hospitals, Premier Purchasing Partners is one of the largest healthcare group purchasing organizations in the United States, offering comprehensive supply chain services to hospitals across the country. Under Alkire's leadership, Premier provides members with innovative programs and services that foster supply chain improvement, promote cost savings and facilitate shared best practices.

"One of our primary functions is to help hospitals accelerate performance for both clinical outcomes and supply chain costs," says Alkire. "We're creating a standard for the sharing of information that can be easily applied and implemented. I really believe that we have to be the ones to drive change — if the stakeholders don't establish the standards, the standards will be chosen for us."

A Model for National Healthcare Reform

In recent years, Premier has led several successful initiatives that have garnered national attention, including the 2003 Hospital Quality Incentive Demonstration (HQID), a pioneering value-based purchasing project with Medicare. More than 250 hospitals with varied demographics participated in the six-year program, which studied quality process measures and outcome statistics. Specific studies examined admission procedures, such as whether cardiac patients were offered aspirin upon arrival, while others analyzed mortality and infection rates. Initially, top-performing hospitals were rewarded while underperforming participants were penalized; midway through the project, performance incentives evolved to include bonuses for various benchmarks and improvements. The program is significant because its results were later used as a model for national healthcare reform.

"We're creating a standard for the sharing of information that can be easily applied and implemented."

"Having anticipated the need for reform nearly a decade ago, we've worked proactively with our members to introduce offerings that would help hospitals reduce readmissions, expand evidence-based care delivery, improve patient safety and eliminate excess costs," explains Alkire. "HQID is one example; another is our acquisition of an automated surveillance system to help hospitals reduce risk and harm."

In fact, Premier houses the nation's largest detailed clinical and financial database, containing patient level data from more than 600 hospitals, 45 million records and 309 million hospital visits. Web-based tools allow hospitals to compare their performance in specific areas to peers and best performers, find opportunities for improvement, and track the results of their efforts. This data warehouse is used by the Food and

Drug Administration for drug surveillance and by the Centers for Medicare and Medicaid Services to evaluate next-generation payment models.

"The value of this platform is in that it allows our hospital members to take a critical look at things like evidence-based outcomes, geographical variations and resource utilization," Alkire says. "Our board of directors has a fundamental belief that the wide variation in how medicine is practiced and how products are used are at the root of the industry's problems. We are focused on tightening up the variations by sharing vital data that can create increased evidence-based outcomes, improved collaboration and more predictable outcomes."

Premier's other recent accomplishments include the "QUEST" collaborative, referred to within the company as "an insurance policy for reform." QUEST helps participating hospitals avoid payment penalties by enhancing quality, reducing readmissions, expanding evidence-based care delivery, improving patient safety, preventing harm and eliminating excess costs. Alkire says in the first 18 months of the project, participants are estimated to have saved more than 14,000 lives and more than $1 billion.

Another alliance effort Alkire is especially proud of is Premier's new Accountable Care Organization (ACO) collaboratives. ACOs connect groups of providers who share the common goal of improving the health status, efficiency and care for specific populations.

"Healthcare is a very fragmented system, and we are actively working to change that," says Alkire. "We are in a unique position because we have 2,400 member hospitals; this allows us to leverage our influence and share best practices in a timely fashion, and the timely sharing of information leads to innovation. We also have a voice and a measure of influence at the federal level, especially when it comes to how certain reform programs are rolled out and implemented. Our members recognize the inherent value in that."

Identifying the Big Picture Challenges

In looking at some of the big picture challenges within the healthcare industry, Alkire identifies two major issues: the lack of shared interests within U.S. hospitals and the overall cost of healthcare currently weighing on the federal budget. "I think everyone understands that we cannot continue to pay at the same levels — we have to create a different delivery system," he says. "There is a keyhole we have to squeeze through before we successfully make that transition, and some stakeholders will have to temporarily defer their own personal profit for the greater good."

I have a passion for communicating ideas in a way that is not dictatorial, but rather inspires action."

A hands-on leadership style drives Alkire to spend a majority of his time on the road interfacing with Premier's members and business partners in an effort to better understand their issues and gather valuable input. When he's not traveling, Alkire motivates his leadership team by continually sharing and modeling the company vision and purpose "to improve the health of communities." In terms of company culture, Alkire says he strives to create an atmosphere where opinions and ideas are welcomed and implemented. "We recognize innovation, while also placing a high value on performance and execution," he says. "I have a passion for communicating ideas in a way that is not dictatorial, but rather inspires action." ❖

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

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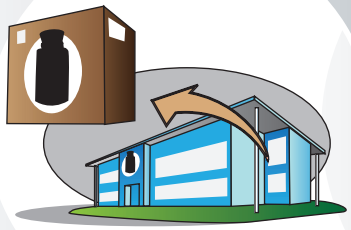

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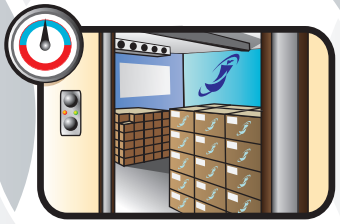

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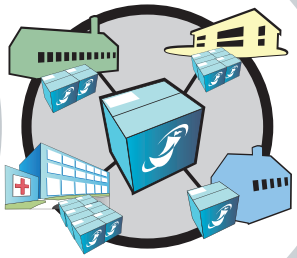

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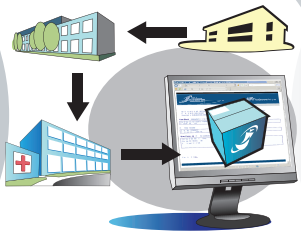
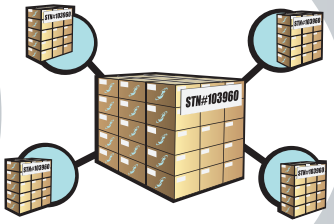
METHODS OF DELIVERY
Monitoring and adjusting for extreme weather conditions allow time-sensitive delivery to ensure product integrity.



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.

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On the Road to Recovery

When a rare disease nearly sidelined Andrew Green, off-label use of immune globulin restored his health and inspired him to become an advocate for patients facing similar challenges.

by TRUDIE MITSCHANG

AT AGE 67, Andrew Green is more physically fit and active than many people his age. The retired entrepreneur practices tai chi five days a week and embarks on daily bike rides — that is, when he's not globe-trotting with his wife, Judy. The couple's travels have taken them to such exotic locales as Japan, Mexico and, most recently, Barcelona. A glance at his day planner would never even hint that Green lives with a rare and debilitating chronic illness that just a few years ago nearly killed him.

Green was diagnosed with central nervous system vasculitis (CNSV) in 2001 at age 58. An avid runner and cross-country skier, Green first sensed something was amiss when he developed sudden-onset fatigue and body aches that shortened his runs and eventually made it difficult for him to simply walk around the block. His health continued to deteriorate until one afternoon he became disoriented during a conversation with his wife and put his head down on the kitchen counter to try to sleep. Alarmed, his wife rushed him to the emergency room at the Cleveland Clinic, where his symptoms prompted doctors to run dozens of invasive tests, but ultimately offered few clues as to what was actually wrong with him.

Since his diagnosis with central nervous system vasculitis, Andrew Green and his wife, Judy, have traveled across the world.

"I was fortunate that there was a doctor from the rheumatology department working that evening," recalls Green. "After I was admitted to the hospital, I underwent eight spinal taps, a bone marrow biopsy, brain biopsy, a biopsy on a nerve in my foot, echocardiograms of blood vessels and several MRIs of my head. Unfortunately, there was no conclusive answer about my diagnosis."

It was the beginning of a long and frustrating journey for Green, who endured misdiagnoses for nearly six months, even going to the Mayo Clinic at one point for a second opinion. In the end, a team of specialists finally made the diagnosis of CNSV. During the diagnosis process, it was discovered that Green had several additional autoimmune diseases too, making his treatment plan somewhat complex. Fortunately, his proximity to the renowned Cleveland Clinic afforded him the best possible care.

Vasculitis Statistics

Vasculitis is considered a rare or "orphan" disease affecting fewer than 200,000 people in the United States. Some quick facts about vasculitis:

- The disease can occur at any age; however, it has its peak in the fourth or fifth decade of life.
- It affects males and females equally.
- Eighty-five percent of patients are older than age 19.
- The currently reported age range of patients is 5 to 91 years.
- The mean age of patients is 41.
- Ninety-seven percent of all patients are Caucasian, 2 percent are black, 1 percent are of another race.

In terms of specific disease states, occurrence rates in the U.S. are:

- Giant cell arteritis: 20 out of 100,000
- Hypersensitivity angiitis: 6 out of 100,000
- Polyarteritis nodosa: 3 out of 100,000
- Takayasu's arteritis: 1 out of 100,000
- Wegener's granulomatosis: 3 out of 100,000 (the exact number of patients is not known, but a very rough estimate is two new cases per million Americans per year, or about 500 new cases diagnosed each year.)

After undergoing various treatment options with limited improvement, Green's doctors prescribed off-label use of intravenous immune globulin (IVIG) to boost his immune system; within a week, he finally began to feel better. Green started with twice-monthly infusions and now infuses every six weeks. He says the treatment has given him back a quality of life he thought was gone forever.

"My life seems normal now," he says. "I'm active; I exercise; I enjoy woodworking. The only thing I've had to give up is cross-country skiing — my battery doesn't stay charged long enough for that!"

Understanding Vasculitis

Vasculitis is an inflammation of the blood vessels that causes thickening, weakening, narrowing and scarring. There are many different types of vasculitis, and symptoms often mimic those of other diseases or disorders, which is why it can be so difficult to diagnose.

Vasculitis can be acute or chronic, and so severe that the tissues and organs supplied by the affected vessels don't get enough blood. The shortage of blood can result in organ and tissue damage, and even death. The signs and symptoms of vasculitis vary, depending on which blood vessels and organ systems are affected. However, general signs and symptoms that most people with vasculitis experience include fever, fatigue, weight loss, muscle and joint pain, loss of appetite and nerve problems, such as numbness or weakness. The main goal of vasculitis treatment is to stop the inflammation. And, steroids and other medicines to stop inflammation are often prescribed.

Advocating Awareness

Never one to sit around and feel sorry for himself, Green keeps busy as an active member of the Education Awareness Council representing CNSV, where he dedicates his time to helping patients get a quicker, more accurate diagnosis for vasculitic diseases. He also finds it rewarding to encourage those who have already been diagnosed. "It's not uncommon to hear you'll be dead in six months once you get this diagnosis," he explains. "It is so rare and you feel so alone — even doctors know very little about it. It's important to provide a forum and a platform for patients to connect with one another for advice and encouragement. It helps me to know I am a shoulder to lean on for someone who is just learning about vasculitis."

Now being treated with IVIG, Andrew is back to doing the things he loves, including exercise and woodworking.

Green says if he's learned anything during this journey, it's that getting one doctor on your team to act as your "quarterback" can significantly help weed through the complex procedure and treatment options. He also advises patients to educate themselves about their disease state. "When it comes to rare diseases, knowledge really is power," he says. ❖

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

After undergoing various treatment options with limited improvement, Green's doctors prescribed off-label use of intravenous immune globulin (IVIG) to boost his immune system; within a week, he finally began to feel better.

Vasculitis Resources

Cleveland Clinic Center for Vasculitis: my.clevelandclinic.org/rheumatology_immunology/vasculitis_center/default.aspx

The Johns Hopkins Vasculitis Center: www.vasculitis.med.jhu.edu

The Mayo Clinic: www.mayoclinic.com/health/vasculitis/DS00513

Vasculitis Foundation: www.vasculitisfoundation.org

BioResearch

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

Literature Review Supports Efficacy of IVIG in Mucocutaneous Blistering Disease

Noting that intravenous immunoglobulin (IVIG) is increasingly used off-label in the treatment of autoimmune and chronic inflammatory disorders, these U.S. investigators searched the PubMed database to determine if there is evidence to support the efficacy of IVIG therapy specifically in autoimmune mucocutaneous blistering diseases (AMBDs).

Twenty-three English-language studies, published between May 1999 and April 2010, were identified that met the following criteria: 1) minimum of five patients, 2) diagnosis based on histology and immunopathology and 3) statistical analysis of data for comparison of efficacy provided. One randomized trial was found and all other studies were case series. Data on 260 patients treated with IVIG were analyzed; these included 191 patients with pemphigus and 69 patients with pemphigoid disorders.

Overall, 245 patients showed improvement with IVIG therapy, without a significant incidence of serious adverse effects. IVIG also demonstrated a corticosteroid-sparing effect. The reviewers concluded that "the best available evidence in the literature indicates that IVIG is efficacious and has a good safety profile in the treatment of AMBDs."

Gürcan, HM, Jeph, S, and Ahmed, AR. Intravenous immunoglobulin in autoimmune mucocutaneous blistering diseases: A review of the evidence for its efficacy and safety. American Journal of Clinical Dermatology, *2010, 11(5): 315-26.*

Liquid and Lyophilized IVIG Equally Effective for Maintenance CIDP Therapy

While different IVIG preparations are generally considered to have comparable clinical efficacy, this has never been formally investigated. Some patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have reported that some IVIG brands are more effective than others, according to Dutch investigators.

Twenty-seven patients with active but stable CIDP with an individualized maintenance regimen of Gammagard S/D (Baxter Healthcare) were randomized to receive four infusions of freeze-dried 5% Gammagard S/D or Baxter's Kiovig 10% liquid IVIG. The overall disability sum score (ODSS) was used as the primary outcome scale, with therapeutic equivalence defined as 1 point in mean difference in ODSS between treatment groups.

Repeated measurements analysis of variance, adjusted for baseline ODSS, revealed a clinically insignificant difference of 0.004. Other than a lower occurrence of cold shivers in patients randomized to Kiovig, no differences were found in the occurrence of adverse events. This trial demonstrated equal clinical efficacy between a freeze-dried and a liquid IVIG preparation for maintenance treatment of CIDP.

Kuitwaard, K, van den Berg, LH, Vermeulen, M, et al. Randomized controlled trial comparing two different intravenous immunoglobulins in chronic inflammatory demyelinating polyradiculoneuropathy. Journal of Neurology, Neurosurgery & Psychiatry, *Jun 28, 2010 [Epub ahead of print].*

Low-Dose Immune Tolerance Induction Works in Severe Hemophilia A With Inhibitors Below 40 Bethesda Units

Dutch hematologists examined results of 26 years of low-dose immune tolerance induction (ITI) therapy as a treatment regimen for inhibitory alloantibodies against factor VIII in patients with severe hemophilia A. Twenty-one patients were treated with regular infusions of low-dose factor VIII (25 to 50 IU/kg) every other day or three times a week in an attempt to obtain immune tolerance.

In 18 of the 21 patients (86 percent), low-dose ITI was successful. A successful outcome was associated with both a pre-ITI titer and a maximum titer during ITI below 40 Bethesda Units (BU)/mL ($P = 0.003$). The time to success was also significantly shorter if the maximum titer during ITI was below 40 BU/mL ($P = 0.04$). In patients with low titer inhibitors (<5 BU/mL), this effect was even stronger ($P = 0.033$).

The investigators suggest that all patients with severe hemophilia A and a pre-ITI inhibitor titer below 5 BU/mL should be treated with low-dose ITI therapy, and those with pre-ITI titers below 40 BU/mL may also strongly benefit.

Ter Avest, PC, Fischer, K, Gouw, SC, et al. Successful low dose immune tolerance induction in severe haemophilia A with inhibitors below 40 Bethesda Units. Haemophilia, *May 2010, 16(102): 71-9.*

KEITH BERMAN, *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Berman previously worked in product development, reimbursement development and market research roles at Baxter Healthcare, Siemens Medical and MiniMed Technologies (now a Medtronic division). Since 1989, he has also served as editor of* International Blood Plasma News, *a blood products industry newsletter.*

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BioProducts

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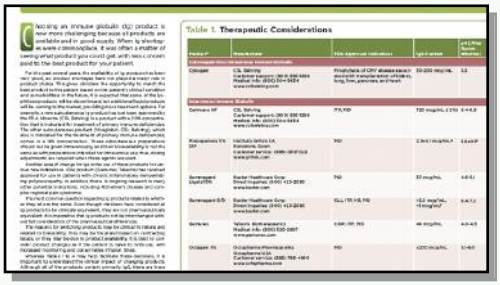
Evaluaide is a health managememt platform that combines predictive modeling and individualized outreach programs. The platform takes members' health data, including past claims and medical records, and processes it through a comprehensive health analysis that confidentially assesses each member's health risks. Members who are at highest risk for serious health issues are identified, and from there, a suite of proactive health advocacy services, including personal wellness coaching, becomes available.
MagnaCare, (888) 799-6465, www.magnacare.com/clients/evaluaide.aspx

IVIG Mobile Application

Immune Globulins: Therapeutic, Pharmaceutical, Cost, and Administration Considerations is now available as a free downloadable application for the iPhone/iPod Touch, Blackberry and java-enabled phones. The information in the application, provided as an educational service from CSL Behring, is intended for pharmacists and physicians and includes therapeutic, pharmaceutical and cost considerations for all IVIG and SCIG products, as well as log reduction factor comparisons.
McMahon Publishing, www.pharmacypracticenews.com



Pharmacy Support Program

PharmacyConnect offers a comprehensive mix of Premier technologies and solutions to help pharmacy directors, clinicians and purchasing staff make decisions regarding the best way to manage their pharmacy operations. Included is PharmacySpend, which allows users near real-time analysis of pharmaceutical purchasing patterns; Supply Chain Advisor, which analyzes all purchases and manages contracts online with access to expert support; SupplyFocus, a comparative database of supply chain cost information for acute care hospitals; SafetySurveillor Pharmacy, which helps clinicians increase efficiency and positively impact the care of more patients; QualityAdvisor, which measures and analyzes performance; OperationsAdvisor, which provides productivity monitoring, assessment and comparative data; and MyPremier, a portal that provides users with a single, consistent point of access to all Premier products, tools and applications.
Premier Healthcare Alliance, (877) 777-1552, www.premierinc.com

SES Update for CNS Clinical Trials

Eviti provides oncologists and insurers access to an independent, nonproprietary oncology treatment library of nearly 1,000 of the most appropriate, proven treatment options covering all modalities for more than 120 cancer types. The program's web-based decision-support engine and comprehensive treatment knowledge-base automatically align the prescription of quality treatment with each patient's insurance plan language at the point of prescribing. It is intended to provide more efficient communication between oncologists and payers, to reduce barriers to information flow and to synchronize treatment decision with treatment authorization and reimbursement. If a physician chooses a regimen that is outside the patient's insurance plan, the program will facilitate a resolution with the insurance company. Eviti can be used as a web-based application or as an integrated component within electronic health records software.
ITA Partners Inc., (215) 569-0656, www.itapartners.com/eviti

Telemedicine

Telemedicine allows patients to visit with physicians live over video for immediate care or capture video/still images, and patient data are stored and sent to physicians for diagnosis and follow-up treatment at a later time. Telemedicine comes in several models, including real time (the most common), store and forward (used when both health providers are not available or not required at the same time), teleradiology (over low or high bandwidth) and home health telemedicine (for outpatients placed under general observation after a surgery or other medical procedure). The three top current uses of telemedicine are radiology, dermatology and psychiatry. A Telemedicine Worldwide Provider Directory includes listings of manufacturers, healthcare providers, education programs and resources.
Telemedicine.com Inc., (530) 676-0421, www.telemedicine.com

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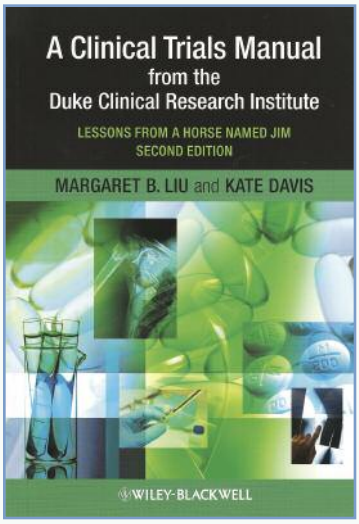
Recently released resources for the biopharmaceuticals marketplace.



Clinical Trials Manual

Published in January, *A Clinical Trials Manual from the Duke Clinical Research Institute: Lessons from a Horse Named Jim* (2nd edition), provides a practical nuts-and-bolts approach to the process of conducting clinical trials, identifying methods and techniques that can be replicated at other institutions and medical practices.

The manual begins with an overview of the historical framework of clinical research and leads the reader through a discussion of safety concerns and resulting regulations. Topics include good clinical practice, informed consent, management of subject safety and data, as well as monitoring and reporting adverse events.

Updated to reflect recent regulatory and clinical developments, the manual reviews the conduct of clinical trials research in an increasingly global context. This new edition has been further expanded to include in-depth information on conducting clinical trials of medical devices and biologics; the role and responsibilities of institutional review boards; and recent developments regarding subject privacy concerns and regulations. It is written for investigators, research coordinators, CRO personnel, students and others who have a desire to learn about clinical trials.
www.wileyblackwell.com; www.interscience.wiley.com

FDA Guidance for Cell-Based Vaccine Development

The U.S. Food and Drug Administration (FDA) has issued final guidance to help manufacturers who are developing safe and effective cell-based viral vaccines to address emerging and pandemic threats. Titled *Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indication*, the document will aid manufacturers who wish to use new cell substrates for vaccine production, such as for influenza vaccines. Currently, all licensed influenza vaccines are produced in chicken eggs.

FDA scientists spent more than a decade conducting the research required for the document, as well as consulting with other scientists, the vaccine industry and the public. In addition to providing advice to manufacturers about the scientific principles of cell substrate development, the guidance describes tests that may be used to evaluate cell substrates intended for use in viral vaccine production. The guidance supplements recommendations on the production of viral vaccines for the prevention and treatment of infectious diseases provided in International Conference on Harmonization (ICH) documents Q5A and Q5
www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM202439.pdf

Global Blood Plasma Market Report

With the global plasma market more than doubling over the period 2000 through 2008, the *Global Blood Plasma Market* report by Koncept Analytics covers the overview, market size and segmentation of the global blood plasma market, including the various drivers, opportunities and challenges faced by the market. Also included is a competitive scenario, company profiles and a market outlook. A number of charts are included, as well as tables, such as the average industrial yields for main plasma proteins, a comparison of blood products utilization and yearly consumption of the plasma products per million people.
www.konceptanalytics.com/reportDetail.aspx?reportID=210

Autoimmune Diseases of the Endocrine System

This comprehensive, easy-to-read discussion of the organ-specific autoimmune endocrine diseases emphasizes new contributions and trends for research and management. It begins with a brief chapter introducing the general principles of immunology, followed by discussions covering topics such as immunogenetics and animal models and how they can be applied toward interpreting human autoimmune endocrine diseases, autoimmune thyroid diseases, insulin-dependent diabetes mellitus hypophysitis, and Addison's disease. The book also discusses future trends toward gaining an understanding of these disorders and possible therapeutic principles. The book is intended as a reference source for internists, endocrinologists, and postgraduate students interested in human autoimmune endocrine diseases.
www.crcpress.com

BioDashboard

CALCULATOR

IVIG Reimbursement Calculator

Product	Manufacturer	HCPCS	Medicare Reimbursement Rates: Hospital Outpatient ASP+4% (per gram)	Medicare Reimbursement Rates: Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$57.693	$58.802
FLEBOGAMMA 5% DIF	Grifols	J1572	$70.904	$72.268
GAMMAGARD LIQUID	Baxter BioScience	J1569	$75.539	$76.992
GAMMAGARD S/D	Baxter BioScience	J1566	$57.693	$58.802
GAMUNEX	Talecris Biotherapeutics	J1561	$73.871	$75.292
PRIVIGEN	CSL Behring	J1459	$70.178*	$70.178

Rates are effective October 1, 2010 through December 31, 2010.
Calculate your reimbursement online at www.FFFenterprises.com.

*Payment rate reflects manufacturer-reported ASP + 6%; based on Medicare transitional pass-through status.

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%)	5 g, 10 g	Bio Products Laboratory	PIDD
HIZENTRA (Liquid, 20%, SCIG)	5 mL, 10 mL, 20 mL	CSL Behring	PIDD
PRIVIGEN (Liquid, 10%)	5 g, 10 g, 20 g	CSL Behring	PIDD, ITP
VIVAGLOBIN (Liquid, 16%, SCIG)	3 mL, 10 mL, 20 mL	CSL Behring	PIDD

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

Injectable Influenza Vaccine

Administration Code: G0008 Diagnosis Code: V04.81

Product	Size	When Administered to Indicated Age Group	CPT Code
FLUZONE Pediatric	0.25 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90655
AFLURIA	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
FLUZONE	0.5 mL single-dose vial		
FLUZONE	0.5 mL prefilled syringe		
FLUVIRIN	0.5 mL prefilled syringe		
FLUZONE	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
FLUVIRIN	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to individuals 3 years and older, for intramuscular use	90658
FLUZONE	5 mL multi-dose vial		
FLUZONE High-Dose	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, when administered to individuals 65 years of age and older, for intramuscular use	90662

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 in more FDA-approved indications (CIDP, PI, and ITP)* than any other liquid IGIV[1]

Important Safety Information for GAMUNEX

Gamunex, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, is indicated for the treatment of primary humoral immunodeficiency disease (PI), idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Gamunex does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer.

Gamunex is contraindicated in individuals with acute severe hypersensitivity reactions to Immune Globulin (Human). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV.

Thrombotic events have been reported in association with IGIV. Patients at risk for thrombotic events may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Gamunex is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

In clinical studies, the most common adverse reactions with Gamunex were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP). The most serious adverse reactions were pulmonary embolism (PE) in one subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in one subject (in PI), and myocarditis in one subject that occurred 50 days post-study drug infusion and was not considered drug related (in ITP).

*CIDP=chronic inflammatory demyelinating polyneuropathy; PI=primary immunodeficiency; ITP=idiopathic thrombocytopenic purpura.

Reference: 1. Data on file. Talecris Biotherapeutics, Inc.

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

Please see adjacent page for brief summary of GAMUNEX full Prescribing Information.

Evidence based. Patient proven.

gamunex®
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