April 2010

BioSupply Trends

Special Focus: SAFETY

Quarterly

Bad Medicine

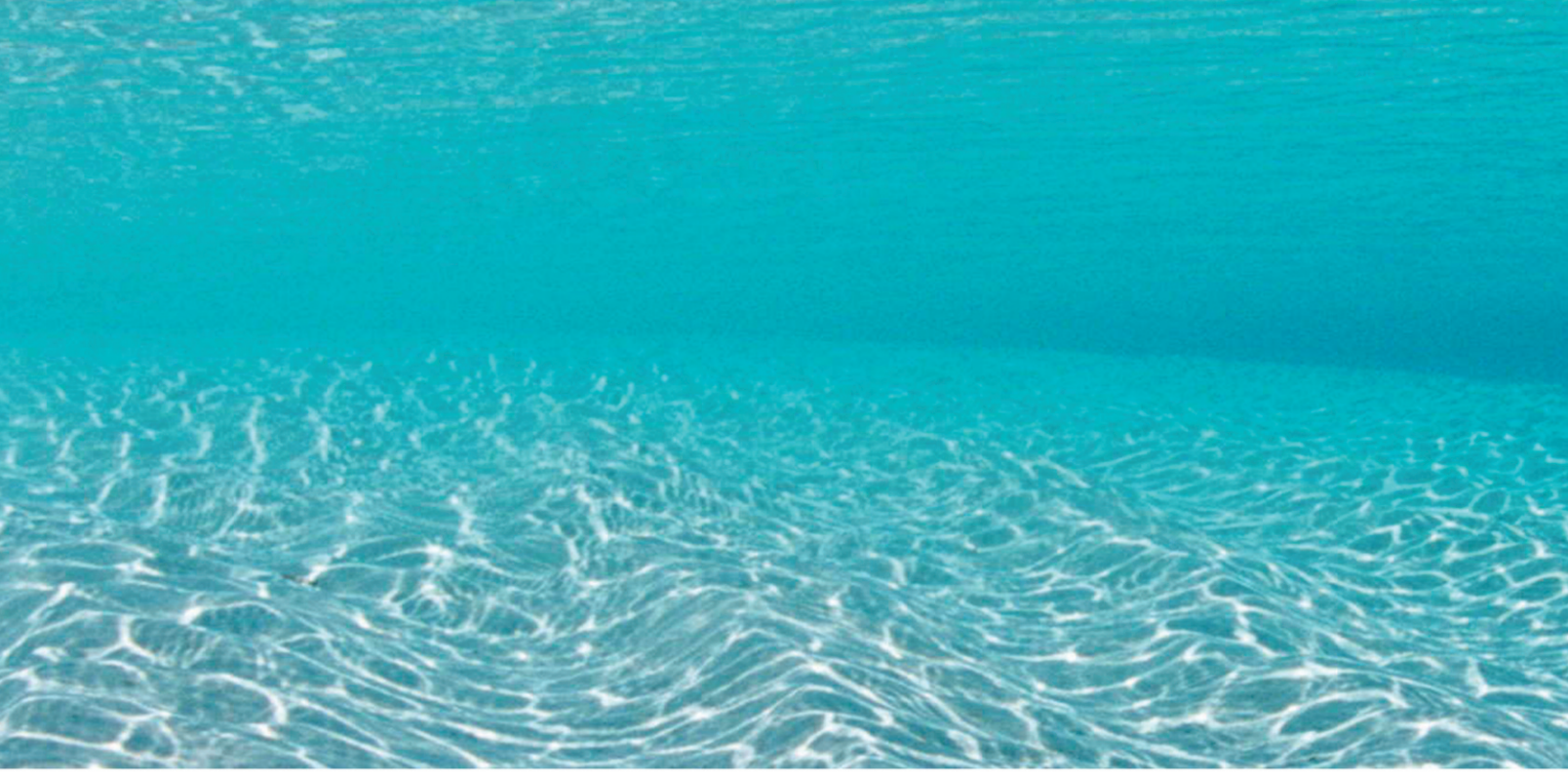
The War on Counterfeiting

Best Practices In Supply Chain Security

FDA Approval: Making Flu Vaccine Safe

Myths and Facts: Rabies | **Preventing Medication Errors**

Counteracting the Anti-Vaccine Movement — Page 38



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

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

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Warnings and Precautions - Hyperproteinemia 8/2008

WARNING: ACUTE RENAL DYSFUNCTION and RENAL FAILURE
See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. octagam® 5% liquid does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

INDICATIONS AND USAGE

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Falsely elevated blood glucose readings may occur during and after the infusion of octagam® 5% liquid with some glucometer and test strip systems.
- Hyperproteinemia, increased serum viscosity and hyponatremia occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome has been reported with octagam® 5% liquid and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infectious agents, *e.g.* viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

HOW SUPPLIED

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

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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

April 2010

Features

Special Focus: Safety

Up Front

BioTrends Watch

BioFocus

BioSources

About BioSupply Trends Quarterly
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Safety First!

LOOKING BACK at the evolution of our company, it's clear that there was a defining moment when what began as a means to an end — an income stream that would allow me to pursue my dream to coach football — turned into to a passion to make a difference in an industry I had, by all accounts, stumbled into. Don't get me wrong, I don't view my entry into healthcare distribution as an accident, but rather a serendipitous event that has challenged, inspired and driven me in ways I could not have foreseen in the beginning.

It was the summer of 1990, at the beginning of the first Gulf War — Desert Storm — when I received a call that created a paradigm shift for me. Our company had just celebrated our two-year anniversary when we learned that the following day, the government was expected to requisition all of the albumin from manufacturers and distributors to treat potential war injuries. I received a call from a potential customer letting me know that another distributor had just called to try to sell it its stock at an inflated price in anticipation of the requisition and expected shortage. Young and a bit naive, perhaps, I was stunned that there was profiteering going on in the healthcare industry during wartime. And it wasn't just the price gouging that was so disturbing; this intentional diversion of product represented a safety risk to those soldiers on the front line. It was at that precise moment that my focus and future inevitably changed; I realized that I wanted to be a part of a solution for an industry that in my mind should always operate with nothing but noble intentions — putting safety and availability, not profits, first. That was the beginning of our commitment to purchase only from legitimate manufacturers, and sell only to certified healthcare providers, shortening the supply chain to avoid secondary distribution channels that open the doorway to counterfeiters and profiteering.

This issue's safety theme takes me back to that moment and the ensuing years of innovation within our own company — as well as collaboration with like-minded companies, individuals, associations and regulating bodies — to influence the change necessary to ensure a safe pharmaceutical supply chain. At FFF, we call this Helping Healthcare Care, which is our mission. The evolution from our initial commitment, to our pledge of Guaranteed Channel Integrity, has resulted in more than 21 counterfeit-free years. Beyond our own sphere of influence, I am proud and overwhelmed by the commitment of our partners, the manufacturers, who put the safety and purity of products at the forefront of their decision-making process. In our Leadership Corner column, Flemming Nielson, president of Octapharma, USA, says it well: "If it's safe for patients, it's safe for the company." I think that all of his industry peers would agree.

The content in this important issue explores the ongoing vulnerabilities in our supply chain and considers meaningful measures to prevent counterfeiting. Surprisingly encouraging is our Industry Insight, which reports on a very positive safety record for plasma products and vaccines during the last five years — a testament to the commitment of multiple stakeholders!

This month's feature on Counteracting the Anti-Vaccine Movement is timely, especially with the recent retraction of an article that appeared in the 1998 British medical journal, *The Lancet*, that shows there is no proven scientific data that supports the author's suggestion that the MMR vaccine will increase the risk of developing autism or any other behavioral disorder. And, our feature on early detection diagnostics for cancer explores many current and developing technologies that have promising potential to improve patient outcomes.

As always, we hope you find this issue insightful and helpful to you and your colleagues. ❖

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

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

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Health Insurance Reform Now Law

On March 23, President Barack Obama signed into law the new healthcare reform legislation titled the Affordable Health Care for America Act.

The landmark bill, passed by the House by a vote of 219 to 212, will provide coverage to an estimated 30 million people who currently lack it. The measure will require most Americans to have health insurance coverage, will add 16 million people to the Medicaid rolls, and will subsidize private coverage for low- and middle-income people. According to the non-partisan Congressional Budget Office, the bill will cost the government approximately $938 billion over 10 years, but it also is estimated to reduce the federal deficit by $138 billion over a decade.

The big changes in the law — those that could affect tens of millions of people — won't take effect until at least 2014. Those include insurance marketplaces called "exchanges," rules requiring insurers to accept all applicants, even those with health problems, and an expansion of state Medicaid programs.

However, those items that do go into effect the first year include:*

New help for some uninsured: People with a medical condition that has left them uninsurable may be able to enroll in a new federally subsidized insurance program that is to be established within 90 days. The legislation appropriates $5 billion for this, although that may not be enough to cover all who apply; it's not clear how much consumers would pay as their share of the cost. Currently, about 200,000 people are covered in similar state programs.

Discounts and free care in Medicare: The approximately 4 million Medicare beneficiaries who hit the so-called "doughnut hole" in the program's drug plan will get a $250 rebate this year. Next year, their cost of drugs in the coverage gap will go down by 50 percent. Preventive care, such as some types of cancer screening, will be free of co-payments or deductibles starting this year.

Coverage of kids: Parents will be allowed to keep their children on their health insurance plan until age 26, unless the child is eligible for coverage through a job. Insurance plans cannot exclude pre-existing medical conditions from coverage for children under age 19, although insurers could still reject those children outright for coverage in the individual market until 2014.

Tax credits for businesses: Businesses with fewer than 25 employees and average wages of less than $50,000 could qualify for a tax credit of up to 35 percent of the cost of their premiums.

Changes to insurance: All existing insurance plans will be barred from imposing lifetime caps on coverage. Restrictions also will be placed on annual limits on coverage. Insurers can no longer cancel insurance retroactively for things other than outright fraud.

Government oversight: Insurers must report how much they spend on medical care versus administrative costs, a step that later will be followed by tighter government review of premium increases. ❖

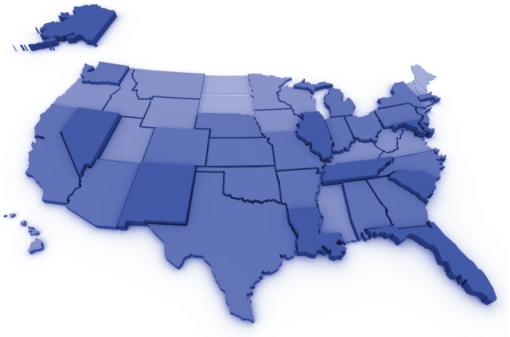
* Appleby, J, and Steadman, K. The Immediate Effects of the Health Reform Bill. *Kaiser Health News*, March 22, 2010.

FDA and EMEA Launch Good Clinical Practices Initiative

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) has launched a bilateral Good Clinical Practices (GCP) Initiative, designed to ensure that clinical trials submitted in drug marketing applications in the United States and Europe are conducted uniformly, appropriately and ethically. The initiative began with an 18-month pilot phase on Sept. 1, 2009, and is focusing on collaborative efforts to inspect clinical trial sites and studies. Products regulated by the FDA's Center for Drug Evaluation and Research in the United States and the EMEA for the European Union will be the focus of the initiative.

Key objectives of the FDA-EMEA GCP initiative will be to conduct periodic exchanges of GCP-related information in an effort to streamline sharing of GCP inspection planning information, and to communicate timely and effectively on inspection outcomes; to conduct collaborative GCP inspections by sharing information, experience and inspection procedures, cooperating in the conduct of inspections and sharing best-practice knowledge; and to share information on interpretation of GCP by keeping each regulatory agency informed of GCP-related legislation, regulatory guidance and related documents, and to identify and act together to benefit the clinical research process. ❖

Insurance Reform Moves to the States



In addition to the new health insurance reform law, states are looking into some of the most important issues that affect patients' access to care. For example, Nebraska has introduced two bills:

LB 1017: An Act to Reform Insurance Prescription Fee Practices

As medical costs escalate in Nebraska and throughout the nation, insurance companies have created a new cost-sharing mechanism known as prescription drug specialty tiers. Most plans have a three-tier structure of fixed-cost benefits to subscribers based upon whether a drug is generic (Tier 1); brand-name preferred (Tier 2); or brand-name non-preferred (Tier 3). But, some insurers also have added fourth and fifth tiers for specialized drugs for serious disorders. This is causing patients who depend on lifesaving, infusible therapies such as biologics, plasma-derived therapies and their recombinants, and interferon, for example, to face even more hurdles. With the new fee structures, these therapies moved from health plans' major medical benefits to specialty tiers with out-of-pocket costs that can range from 10 percent to 50 percent of the cost of the therapy. On average, the plans charge 35 percent of costs under Tier 4, and they charge far more for Tier 5 plans. The cost to the patient, in some cases, can be thousands of dollars per day — a price few can afford.

LB 1017 ensures that every insured Nebraskan has access to reasonable prescription drug benefits by requiring that all health plans delivered or renewed on or after Jan. 1, 2011, meet the following criteria:

- The plans cannot create specialty tiers that require payment of a percentage of prescription costs.
- The plans cannot charge prescription drug copays that exceed the cost of the prescription to the healthcare plan, nor can they charge a copay that exceeds by 500 percent the lowest prescription drug copay in the plan.
- If a health plan includes a limit for out-of-pocket expenses for benefits other than prescription drugs, the plan must include a provision that would result in the lowest out-of-pocket prescription drug cost to the subscriber.
- Either out-of-pocket expenses for prescription drugs would be included under the plan's total limit for out-of-pocket expenses or prescription drugs could not exceed $1,000 per individual or $2,000 per family for the contract year.

LB 1088: Physician and Patient Prescription Protection Act

In Nebraska and throughout the nation, it has become increasingly difficult for patients to obtain the medications their physicians prescribe. Many insurers have taken steps to encourage physicians and patients to switch prescriptions based solely on cost considerations. Increasingly, patients are being forced to switch to drugs that are similar to, but not the therapeutic equivalent of, the prescriptions that their doctors ordered. In many cases, patients and physicians are not told that the substitution has taken place, thereby placing patients' lives in jeopardy. Known as therapeutic substitution, this practice takes patients off of medicines that work well for them and switches them to different medications with different active ingredients that are less expensive, but not necessarily as effective or safe.

LB 1088 would ensure that insurers and pharmacy benefits managers (PBMs) send notifications of request for medication changes to patients and their physicians or other prescribing health professionals whenever the insurer or PBM recommends the change. Among other things, this notification will acknowledge that no medication change will be allowed without the authorization of the original prescribing healthcare professional; clearly identify the originally prescribed medication and the medication to which the patient would be changed; describe any financial incentives that may be provided or offered to the prescribing healthcare professional by the insurer or the PBM; describe any financial incentives that a health insurer or PBM may receive to encourage a medicine exchange; explain any cost-sharing changes for which the patient would be responsible should the medication change take place; and state that the insured has the right to discuss the proposed medication change before it occurs. This bill is important because it will return the dialogue about prescription drug benefits and risks to the patient examining room, where it belongs. Physicians, rather than insurers, best know which treatments will or will not work for their patients. Factoring in the patient's medical history and current condition, physicians can help patients make informed decisions about prescription drug costs, quality and health benefits. ❖

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
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Companies Come to the Aid of Haiti Relief Efforts

It didn't take long after Haiti's catastrophic earthquake for America's pharmaceutical research and biotechnology companies to come to the country's aid. As of this writing, more than $25 million in medicines, medical supplies and cash has been donated to relief efforts, and that amount will undoubtedly continue to rise as these and other companies contribute through both organizational donations and pledges to match employee donations. According to Billy Tauzin, CEO and president of the Pharmaceutical Research and Manufacturers of America (PhRMA), "The day the news broke about the tragedy in Haiti, America's biopharmaceutical companies got to work — coordinating efforts with relief organizations and healthcare groups already on the ground — making sure everything from simple antibiotic creams to critical medicines were made accessible to victims."

Indeed, the list of companies is long and the amount of the donations impressive:

• Through its Foundacion Probitas, a program established in 2008 by Grifols, the company has donated approximately $1.4 million in health materials, including intravenous serum, blood bags and plasma products, such as albumin and specific gammaglobulins.

• GlaxoSmithKline has donated medi-

cines valued at $1.4 million. In addition, the company has committed approximately $408,000 to the British Red Cross to help meet the water and sanitation needs of those affected by the disaster.

• Immediately following the earthquake, Novartis shipped 10 pallets of medicine (antibiotics and analgesics) worth approximately $1.5 million. The company also has pledged more than $2.5 million for direct financial support for relief organizations operating in Haiti, as well as donations of essential medicines.

• Novo Nordisk has donated more than $90,000 to support the relief work of the Danish Red Cross in Haiti. In addition, the company supported the relief organization Project Hope by donating 50,000 vials of insulin.

• Sanofi-aventis has committed $1.4 million in financial aid to long-term reconstruction initiatives and the rehabilitation of the Haiti population. Its initial contribution was to commit $140,000 and considerable donations of medicines and vaccines, which it continues to do. The company also is matching employee donations.

• Bayer provided immediate relief in the form of medicines worth approximately $125,000 to the Red Cross in the Dominican Republic to enable it to be distributed quickly. Bayer also is matching all employee donations.

• Merck made an initial contribution of $450,000 to assist relief efforts. The company also is donating needed medicines through its Merck Medical Outreach Program, and through its partners, it has shipped $2.6 million in market value of donated Merck products. And, it has a gift program to match employees' financial donations.

• Baxter International has committed $1 million to support disaster relief efforts, including $350,000 in grants to support both immediate, acute-care and longer-term needs in the region. Its Employee Disaster Relief Matching Gift Program will match employee contributions. ❖

People and Places in the News

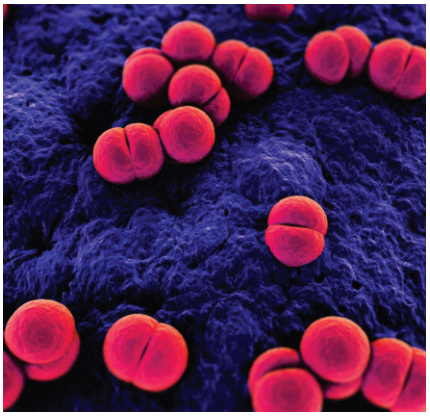
Sanofi-aventis has signed a binding agreement to acquire **Fovea Pharmaceuticals SA**, a privately held French research and development biopharmaceutical company focused on ocular diseases.

The **CSL Behring-Canada Research Chair in Endothelial Cell Biology** has been established to research and develop new therapies for patients with bleeding and immune system disorders. The chair program is a professorship created through the Canada Research Chairs Program, and will be held by the newly appointed director of the CBR, physician-scientist Edward Conway, MD, PhD, MBA.

Human Genome Sciences (HGS) received a $75 million milestone payment from **Novartis** on successful completion of Phase III development with the chronic HVC drug albinterferon alfa2b and the decision to submit regulatory approval applications. The drug (formerly known as Albuferon), a genetic fusion of human albumin and interferon alfa generated using HGS' albumin-infusion technology, will be called Zalbin in the U.S. and Joulferon in the rest of the world.

Medicine

FDA Approves Menveo for Meningococcal Disease



The Food and Drug Administration (FDA) has approved Menveo, a quadrivalent meningococcal conjugate vaccine for individuals 11 to 55 years of age. Manufactured by Novartis Vaccines and Diagnostics, the active immunization prevents invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, Y and W-135. The approval was based on a Phase III clinical trial that showed a higher immune response compared to the other U.S.-licensed ACWY meningococcal vaccine.

Meningococcal disease is a leading cause of bacterial meningitis, an infection of the membrane around the brain and spinal cord, which infects more than 500,000 people each year and leads to more than 50,000 deaths globally. In the U.S., the incidence of meningococcal disease ranges between 1,000 and 3,000 cases per year. Since 2005, the Advisory Committee on Immunization Practices has recommended routine immunization with a quadrivalent meningococcal conjugate vaccine for all adolescents 11 to 18 years of age, college freshmen living in dormitories and people in other high-risk groups who are 19 to 55 years of age.

"The FDA approval of Menveo is an important milestone for adolescent immunization in the U.S.," says Andrin Oswald, division head of Novartis. "According to CDC estimates, approximately 16 million adolescents between the ages of 11 and 18 are at risk and remain unprotected against meningococcal disease."

The Menveo development program for other age groups continues in multiple Phase III clinical trials. Data to support an indication for children ages 2 through 10 is expected to be submitted in the first half of 2010, and Novartis expects to file data to support an infant indication in 2011. ❖

Medicine

CSL's Hizentra SCIG Receives FDA Approval

CSL Behring has received Food and Drug Administration approval for its Hizentra immune globulin (IG) subcutaneous (human) 20% liquid for treating patients diagnosed with primary immunodeficiency (PI). The once-weekly IG replacement therapy is the first 20 percent subcutaneous IG (SCIG) approved in the U.S.

Hizentra is a high-concentration product stabilized with L-proline, a naturally-occurring amino acid. It can be stored at room temperature, requiring no refrigeration, making it ready to use by patients who can safely self-administer it. "As the first SCIG treatment with a 20 percent concentration of immunoglobulin, Hizentra represents an effective, convenient choice of at-home IG therapy that will allow people with PI to schedule treatment around their busy lives, instead of scheduling their lives around treatment," says Robert Lefebvre, vice president and general manager, U.S. Commercial Operations at CSL Behring. ❖

Medicine

FDA Approves Octapharma's wilate

The U.S. Food and Drug Administration (FDA) has approved wilate for the treatment of spontaneous and trauma-induced bleeding episodes in patients with all types of von Willebrand disease (VWD). Developed by Octapharma, the new high-purity, double-virus inactivated von Willebrand Factor/Coagulation Factor VIII Concentrate (Human) demonstrated efficacy for all types of VWD, including pediatric patients, in four prospective clinical trials utilizing both objective and subjective criteria.

VWD is the most common bleeding disorder and is found in approximately 1 percent to 2 percent of the U.S. population, according to the Centers for Disease Control and Prevention. The FDA approval of wilate marks the entrance of Octapharma USA into the U.S. blood coagulation market, with product availability scheduled for early 2010. ❖

Did You Know?

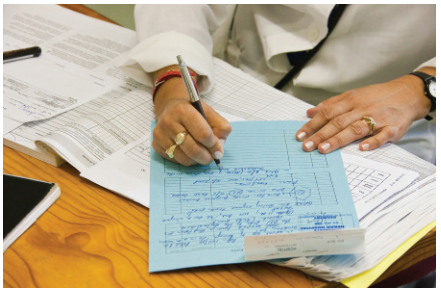
"There are nearly 3,000 cases of meningococcal disease every year in the U.S., [and] between 10 and 12 percent of the cases are fatal. Among those who survive meningococcal disease, approximately 20 percent suffer long-term consequences, such as brain damage, kidney disease, hearing loss or limb amputations."

— National Meningitis Association

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

What is considered good documentation?



Proper and complete documentation can help avoid insurance denials and delays. When writing a letter of necessity, it is helpful to reference the insurance policy. Documentation should address the insurance policy's qualifications for treatment. In general, proper documentation should include:

- a patient history and physical
- physician office/progress notes
- test results with written interpretation
- accurate patient weight in kilograms
- documentation of prior treatment therapies and results
- evidence of blood level results that demonstrate a specific deficiency or disease
- history of recurrent and severe infections (when appropriate for the diagnosis); this includes chart notes, culture reports, lab results and radiological confirmation of infections. (Some insurance policies and Medicare local coverage determinations specifically state that calling in a prescription for antibiotics is not proof of infection.)
- current effectiveness of therapy
- goals and/or treatment plan

It also is helpful to provide specific medical studies supporting the treatment plan.

What do insurers routinely require for the coverage of a C-1 inhibitor to treat hereditary angioedma (HAE)?

Until recently, there were few effective treatments for patients in the United States suffering with HAE to prevent or stop severe swelling and pain brought on by attacks. Physicians now have the option to treat patients with three new medications:

1. Berinert by CSL Behring, which is FDA-approved for treating acute laryngeal and abdominal HAE attacks
2. Cinryze by ViroPharma, which is indicated for the routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE
3. Kalbitor by Dyax, which is FDA-approved to treat acute HAE attacks in patients 16 years of age and older

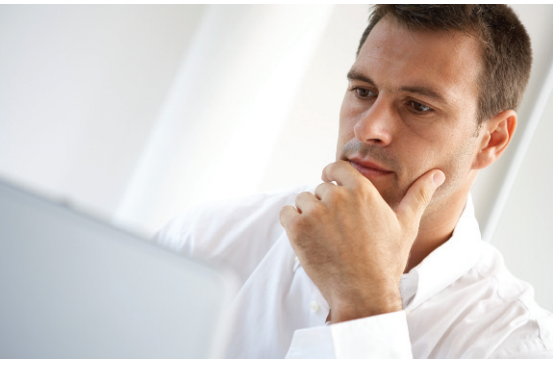
As with all expensive treatments, most insurers require a preauthorization before they will approve the start of treatment with a C-1 inhibitor. Providers must submit documentation that supports the diagnosis. According to one major insurer, documentation about the patient should include:

- antigenic C-1 inhibitor, functional C-1 inhibitor and C-4 levels
- history of frequent or severe attacks
- previous treatment failure or contraindication to Danazol or Stanozolol

In addition, reauthorization requests should include documentation showing a decrease in attacks and/or severity of attacks.

Will insurers or Medicare cover IVIG for polymyositis or dermatomyositis?

Yes. Immune globulin (IG) treatments for dermatomyositis and polymyositis are covered disease states, but not as a first line of therapy. In general, insurers and Medicare look for documentation that shows other treatments have been tried and have failed. Patients must be unresponsive to steroids and immunosuppressants, intolerant to steroids and/or immunosuppressives, or have serious side effects from steroids and/or immunosuppressives. For continued IG treatment, a patient's record must show that there was a measurable response within six months of infusing IG, or its use will no longer be considered medically necessary.



What are the key issues to consider when choosing factor (blood clotting) products?

Treating one hemophilia patient can cost hundreds of thousands of dollars each year, and, in especially severe cases, that amount can be reached each month. Understandably, these high-dollar cases draw passionate attention from providers, patients, manufacturers, case managers and insurers. Except when considering lifetime caps, cost may not be the biggest driver behind product choice for the patient. Because many hemophilia patients will reach their yearly out-of-pocket maximums before the flowers bloom in the spring, their yearly out-of-pocket requirements are met early, and costs beyond those requirements do not influence product choice, unless they affect their lifetime cap. Many hemophilia patients understand that being well-educated about their treatment is essential to successful treatment and preservation of good health. Their chief concerns about coagulation products include:

- shelf-life with and without refrigeration
- whether one product works better than another
- safety track record of the manufacturer
- diluent quantity per vial and/or dose (many patients feel less is best)
- vial size (fewer vials means less storage space and less time spent on treatment preparation)
- derivation: recombinant or human plasma-based

Unlike many other disorders, however, there appears to be few, if any, official formularies regarding choice of products for hemophilia. Like other well-known plasma products, there are no generics — only brand-named products. While many insurers do place factor products in a Tier II or III level of reimbursement, most put all brands on one tier level, usually the higher tier. Regardless of the apparent lack of formulary policies that frequently drive brand choice, patients report being asked to switch brands by both insurers and providers.

When a provider or patient is asked to switch brands, it is important to ask questions and get answers before changing. For instance, they should ask why the brand switch is being requested and who is making the request, and how the change will affect the patient. They should also ask to receive the policy and the request to change brands in writing, and the patient should receive copies, too. In the end, how well the patient responds and follows treatment is ultimately what is going to be most cost-effective for all concerned.

What are the qualifiers insurers consider medically necessary to treat alpha-1 antitrypsin deficiency (AAT) with an alpha 1-proteinase inhibitor?

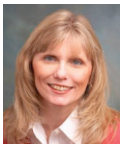
Alpha-1 antitrypsin deficiency (AAT) is an inherited disorder that can cause lung disease in adults and liver disease in adults and children. Symptoms of AAT include wheezing, difficulty breathing, shortness of breath, unintentional weight loss, fatigue, recurrent respiratory infections, a barrel shaped chest and a chronic cough.

Delayed or poor treatment can lead to permanent disability and premature death. Patients with this type of deficiency are often misdiagnosed as having chronic obstructive pulmonary disease (COPD) or asthma. The World Health Organization recommends all patients diagnosed with COPD or asthma be tested for AAT.

The following is an excerpt from one major insurer's policy detailing what documentation warrants treatment of AAT with an alpha-1 proteinase inhibitor:

- the patient's alpha1-antitrypsin (AAT) concentration must be less than 80 milligrams per deciliter (mg/dl) [or greater than 11 micromolar (μM)]
- the patient's obstructive lung disease, as defined by a forced expiratory volume in one second (FEV1) of 30 percent to 65 percent of predicted or a rapid decline in lung function, must be defined as a change in FEV1 of greater than 120 mL/year
- the patient must be a non-smoker

For a list of standards of diagnoses and management of patients with AAT, go to http://www.alpha-1foundation.org/healthcare/?c=03-ATSERS-Standards-PDFs. ❖



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

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

Are *you* a Face of Influenza?

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

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

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

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

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

AMERICAN LUNG ASSOCIATION®

FACES OF INFLUENZA™

American Lung Association's Influenza Prevention Program

In collaboration with sanofi pasteur

www.facesofinfluenza.org

Are You a "Face" of Influenza?

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

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

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

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

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

FACES OF INFLUENZA™
American Lung Association's Influenza Prevention Program
In collaboration with sanofi pasteur

References

1. Centers for Disease Control and Prevention (CDC). Provisional recommendations forthe prevention and control of influenza (2009-2010 influenza season). http://www.cdc.gov/vaccines/recs/provisional/downloads/influenza-feb-2009-508.pdf. Accessed May 1, 2009. **2.** CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR*. 2008;57(RR-7):1-60.

AMERICAN LUNG ASSOCIATION®

Bad Medicine

The War on Counterfeit Drugs

When it comes to preventing counterfeit drugs from tainting the supply chain, solutions are far from simple. Meaningful preventive measures will require education and legislation on federal and state levels, and within the industry itself.

By Trudie Mitschang

Imagine opening a new tube of toothpaste and winding up with a mouthful of diethylene glycol, a poisonous chemical used in antifreeze. Sounds far-fetched, but that's exactly what happened to consumers in New York, New Jersey, Pennsylvania and Maryland in 2007 when a batch of compromised Colgate toothpaste containing the potentially lethal ingredient turned up in various discount stores. The labels on the toxic tubes claimed they had been manufactured in South Africa (Colgate-Palmolive Co. does not manufacture there).[1]

Best known as an industrial solvent, diethylene glycol is a potential killer. It is frequently used by counterfeiters hoping for a quick profit to replace the safe but pricier ingredient, glycerin. And, in the past few decades, this inexpensive syrup has compromised everything from cough and fever medication to teething formula for infants. In developing countries, at least eight mass poisonings have been linked to diethylene glycol, leading to thousands of deaths, many of them children. While identifying the origin of these counterfeit drugs is difficult, the warmest trails seem to lead to China, a country where safety regulations have yet to catch up with its expanding role as a global pharmaceutical supplier.[2]

The United States also has a history of diethylene glycol-related deaths. In 1937, more than 100 people died after ingesting a product laced with it — an incident that became the impetus behind the 1938 Federal Food, Drug and Cosmetic Act. Now, 70 years later, drug counterfeiters are up to their same tricks, which begs the question: If counterfeit toothpaste has already arrived on our shores, could similarly compromised over-the-counter medicines be far behind?[3]

In an interview with the Partnership for Safe Medicines, Anthony Barron, the European Federation of Pharmaceutical Industries and Associations' coding and identification project coordinator, discussed the prospect of U.S. policymakers considering the importation of medicines as part of healthcare reform.

"U.S. policymakers should proceed cautiously in opening importation of medicines from other countries," Barron stated. "So far, most warnings of counterfeit issues in the U.S. were related to drugs purchased on the Internet, as opposed to supply chain failures — a stark contrast to the cases of counterfeit drugs found in the U.K.'s legitimate supply chain."[4]

The World Health Organization (WHO) estimates that up to 10 percent of globally traded drugs are counterfeit. According to an article published by the Center for Medicine in the Public Interest, worldwide counterfeit pharmaceutical sales are increasing at about 13 percent annually — nearly twice the pace of legitimate pharmaceuticals — and could become a $75 billion industry by the end of this year. That's a 92 percent jump from 2005. Clearly, there is money to be made, and opportunistic criminals are cashing in.[5]

"We've made progress in terms of awareness, but there is still a lot that needs to be done, including federal legislation and more education for both healthcare professionals and consumers," says Katherine Eban, investigative journalist and author of *Dangerous Doses*, an in-depth exposé of counterfeiting operations within the pharmaceutical supply chain. "Since my book was published in 2005, the Food and Drug Administration (FDA) has encouraged the industry to implement electronic pedigrees, but so far, we're only seeing a response at the state level. Drug counterfeiting is a problem that is only going to get bigger as time goes on."

The World Health Organization (WHO) estimates that up to 10 percent of globally traded drugs are counterfeit.

Counterfeits Part of a Broader Problem

WHO defines counterfeit drugs as "those which are deliberately and fraudulently produced and/or mislabelled with respect to identity and/or source." Counterfeits are actually just one part of the broader problem of substandard pharmaceuticals — those products in which the composition does not meet correct scientific specifications and are consequently ineffective and often dangerous to the patient. According to the WHO fact sheet, substandard medicines can result from many factors, including negligence, human error, insufficient resources or counterfeiting. And, both branded and generic medicines can be considered counterfeit or substandard.

A drug may be considered counterfeit for many reasons, including:

- too much or not enough active ingredient
- no active ingredient
- the wrong active ingredient
- dangerous excipients and dyes
- the wrong ingredients, but authentic packaging
- the correct ingredients, but fake packaging
- the wrong ingredients, as well as fake packaging

In today's global marketplace, no one is truly safe from the

effects of counterfeit drugs. It's a growing problem in the United States, Europe, Asia and Africa, with drug counterfeiters actively defrauding consumers and interfering with patient therapies that are necessary to alleviate suffering and save lives. Even if the ingredients are correct, counterfeit packaging may include mislabeling, false expiration dates and inaccurate information about dosage and origin. In any event, the consequences for patients can be deadly. WHO estimates that counterfeit drugs are associated with up to 20 percent of the one million malaria deaths worldwide.[5]

While both industrialized and developing countries are impacted by drug counterfeiting, developing countries typically suffer the highest number of fatalities. For one thing, wealthier countries tend to see more counterfeit drugs pop up in the "lifestyle medication" category, rather than products used to treat life-threatening illnesses. In developing countries, it's just the opposite, with the highest number of pirated drugs being used to treat serious diseases like malaria, tuberculosis and HIV/AIDS.[6]

Counterfeits are actually just one part of the broader problem of substandard pharmaceuticals.

Online Pharmacies: Poison in the Pipeline

Part of the reason counterfeit drugs are so deadly and difficult to detect is that counterfeiters go to great lengths to ensure the pirated product looks identical to the real thing. Last September, 29-year-old University of Maryland pharmacologist Carrie John died following an allergic reaction to a counterfeit version of a drug that was legal in the United States, but had been purchased online from the Philippines by a fellow postdoctoral research student. John was using the narcotic painkiller buprenorphine recreationally, and reports state that the drug she injected so closely resembled the legal version that two pharmacologists couldn't tell the difference.[7]

The H1N1 pandemic of 2009 created a unique opportunity for online criminals. The virus dramatically increased the demand for flu antidotes, and amid early widespread panic, many consumers went online looking for discounts on flu-fighting drugs like Tamiflu, playing right into the hands of waiting criminals. In Europe, Russian crime gangs are said to have raked in millions online by marketing counterfeit Tamiflu to anxious Britons.[8]

Last year in the U.S., the FDA, which continuously monitors the Internet, issued warnings to the producers and distributors of more than 135 products available online that were making false claims regarding the H1N1 virus. The FDA went so far as to buy some of these products to test their claims for accuracy. One product came from India and contained two nondescript white tablets that were sold as a Tamiflu equivalent. Instead of containing the antiviral oseltamivir, the tablets actually contained acetaminophen, the active ingredient in Tylenol. Four other products purchased by the FDA did contain oseltamivir, but in varying doses, which could have been ineffective or even caused dangerous side effects.[9]

Of course, antivirals were not the only flu drugs being peddled online last year. The seasonal flu vaccine, which was in short supply because production capacity was used to create the 2009 H1N1 vaccine, started showing up in various "gray markets" — often being peddled for as much as eight times the manufacturers' original price. An article in the *Cape Cod Times* reported that the pharmacy head at one local hospital was contacted by a so-called secondary wholesaler offering to sell him up to 100 packs of Fluarix for $87 a dose. The vials normally sell for less than $10.[10]

Joining Forces and Fighting Back

Worldwide pharmaceutical counterfeiting may be on the rise, but so are the efforts to stop this insidious crime. Late last fall, Interpol officers in Europe, drug agents in the United States and task forces from Sweden to Singapore joined forces and conducted a series of highly organized raids targeting counterfeit drugs. The crackdown in the United States uncovered more than 700 alleged packages of fake or suspicious prescription drugs including Viagra, Vicodin and Claritin, and shut down 90 alleged rogue online pharmacies. The international operation took down 72 websites, seized nearly 1,000 packages and found more than 167,000 suspected illicit and counterfeit pills.[11]

In other parts of the world, leaders from Benin, Burkina Faso, the Central African Republic, Congo-Republic, Niger and Senegal joined former French President Jacques Chirac in Cotonou, Benin, to campaign against the manufacturing and sale of fake pharmaceuticals.[12] And, in Taiwan, the High Prosecutors Office has formed a task force to crack down on criminal rings selling counterfeit and substandard drugs.[13]

Major pharmaceutical companies also have spearheaded campaigns to tackle the problem. Merck Serono, one of the world's largest pharmaceutical companies, recently began funding the distribution of minilabs in developing countries

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

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

1 INDICATIONS AND USAGE

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

1.1 Primary Humoral Immunodeficiency

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

1.2 Chronic Immune Thrombocytopenic Purpura

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

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

5.2 Renal Failure

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

5.3 Hyperproteinemia

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

5.4 Thrombotic Events

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

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

5.5 Aseptic Meningitis Syndrome (AMS)

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

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

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

5.6 Hemolysis

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

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

5.7 Transfusion-Related Acute Lung Injury (TRALI)

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

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

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

5.8 Volume Overload

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

5.9 Transmissible Infectious Agents

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

5.10 Monitoring: Laboratory Tests

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

5.11 Interference With Laboratory Tests

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Treatment of Primary Humoral Immunodeficiency

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

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

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

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

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

*Excluding infections.

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

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

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

* Two consecutive daily infusions.

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

6.2 Postmarketing Experience

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

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

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

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Use of Privigen in nursing mothers has not been evaluated.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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to improve detection of fake ingredients in drugs used to combat malaria, HIV and tuberculosis.[14] And, Pfizer has begun implementing safer packaging, using radio-frequency-identification tags on its popular Viagra blockbuster packs.[15]

In late 2009, a group of companies and associations from all facets of the pharmaceutical industry teamed up to form RX-360, an international consortium aimed at securing the performance of the supply chain and making it easier for suppliers to share and receive information. To date, member companies include biopharmaceutical manufacturers like AstraZenica, Merck and Sanofi; suppliers such as West, Merck, KGaA and SAFC; and various trade organizations and independent auditing firms, including the European Generic Medicines Association. The consortium's mission is to "create and monitor a global quality system by adopting standards and best practices for the supply chain, supporting technology developments for supply-chain security, monitoring the supply chain, and developing shared audit programs."[16]

The Consumer Component: An Issue of Supply and Demand

Pharmaceutical counterfeits impact individuals and industry throughout society — not just patients at the end of the supply chain. Healthcare organizations, governments and even entire countries pay the price when counterfeiting is allowed to proliferate. Last year, the FDA launched the Secure Supply Chain pilot program, designed to protect pharmaceuticals and their ingredients that are produced outside of the U.S. Additionally, the FDA has opened offices in India and China in an attempt to better monitor the increasing numbers of pharmaceutical manufacturers in those countries.[17] While these are clearly steps in the right direction, the problem of supply chain safety is not simply about supply; it's also about demand.

The fact remains that consumers continue to make purchases outside of the secure supply chain, enticed by the availability of hard-to-find drugs and gray market pricing. From travelers restocking their medicine cabinets while on vacation to Internet shoppers hoping to score deep discounts on pricey lifestyle medications, purchasing abroad has a high level of consumer appeal. According to the Congressional Budget Office, brand-name drugs on average cost from 35 percent to 55 percent less in other industrialized nations than they do in the U.S.[18]

That's why education about the risks associated with these types of transactions needs to increase. And while some U.S. consumers may develop a false sense of security when purchasing from neighboring Canada, a 2005 FDA drug bust indicates that nothing could be further from the truth. The operation — in which the agency examined nearly 4,000 packages at airports in New York, Miami and Los Angeles — found that 85 percent of the drugs ordered from what customers believed were Canadian pharmacies actually came from 27 other countries. Not surprisingly, a number of the products also were found to be counterfeit.[19]

The road ahead in the war on counterfeit drug trafficking will not be an easy one; there are no simple solutions. Organized efforts by pharmaceutical companies, government agencies and consumer groups will need to pursue improved education and legislation to weed the poison out of the pipeline and create a safe, secure supply chain. ❖

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Preventable Harm: Averting Medication Errors

By Trudie Mitschang

To err may be human, but when it comes to medication mistakes, the consequences can be deadly. Remedying the problem will require coordinated interventions across all sectors of the healthcare system.

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer."

With as many as three billion prescriptions written annually, and most with no adverse consequences to the patient, you might assume that medication mistakes are a rare occurrence. But a 2006 study conducted by the Institute of Medicine turned up some stark statistics: The error rate in administering medication in U.S. hospitals averages one patient per day, and nearly 1.5 million people per year are harmed by medication mistakes. The report went on to state that although the vast majority of errors do not lead to fatalities, at least 7,000 deaths were attributed to drug overdoses and other medication mishaps. And, while hospital-based errors are the easiest to trace and document, hospitals are certainly not the only setting in which this problem exists. Medication errors can occur in any place that medication is administered or dispensed: physicians' offices, outpatient surgery centers, nursing homes, urgent care centers and even pharmacies.

Most Common Medication Errors

According to the American Hospital Association, the most common types of medication errors include:

- incomplete patient information (not knowing about patient allergies, other medicines they are taking, previous diagnoses and lab results);
- unavailable drug information (such as lack of up-to-date warnings);
- miscommunication of drug orders stemming from poor handwriting, confusion concerning drugs with similar names, misuse of zeroes and decimal points, confusion of metric and other dosing units and inappropriate abbreviations;
- lack of appropriate labeling as a drug is prepared and repackaged into smaller units; and
- environmental factors, such as lighting, heat, noise and interruptions, that can distract health professionals from their medical tasks.

Clearly, medication mistakes can occur at many junctures in the pharmaceutical supply chain for a variety of reasons. Some mix-ups are fairly benign while others result in unnecessary loss of life. All are troubling.

"When my 19-year-old son broke his leg, the drugstore pharmacist typed the incorrect dosage information on his codeine prescription," recalls Temecula, Calif., resident Kevin Vaughn. "Instead of prescribing one to two tablets every four hours, the label said to take 11 tablets every four hours. My son had taken nine tablets by the time I discovered the error. I immediately had him throw them up and took him to the emergency room, where they pumped his stomach. He's fine now, but the doctor said the mistake could have severely damaged his liver."

Another error took place when staff members at a Wellesley, Mass., school went to get 2009 H1N1 vaccinations in early January. But, instead of the 2009 H1N1 vaccine, they received a shot of insulin. While the staffers suffered no long-term damage, the potential for serious complications clearly existed. It was determined that a school nurse was responsible for giving patients the wrong injection.

With as many as three billion prescriptions written annually, and most with no adverse consequences to the patient, you might assume that medication mistakes are a rare occurrence.

In another well-publicized case last fall, actor Dennis Quaid's newborn twins were accidentally given 1,000 times the intended dosage of heparin, a medication used to prevent blood clots around intravenous catheter sites. News reports stated that nurses at a Los Angeles hospital mistakenly administered heparin with a concentration of 10,000 units per milliliter instead of the prescribed 10 units per milliliter. The twins survived, but not all families are as fortunate.

A lawsuit is currently pending against Rite Aid drugstores claiming pharmacists were negligent in issuing a lethal dose of a chemotherapy drug. The deceased patient's family says the prescription instructed the patient to take 14 capsules of the medication by mouth daily, 10 times the usual dose and almost double what is known to be fatal.

Minimizing "At-Risk Behaviors" by Healthcare Professionals

A white paper issued by NCC MERP acknowledges that it is human nature to look for faster and easier ways to accomplish tasks. A problem arises, however, when physicians, pharmacists and other healthcare professionals engage in such behavior, as it can put patients at risk. The report identifies rushing to complete tasks as one of several "at-risk behaviors" practitioners may engage in because the rewards are immediate and the risk of patient harm seems remote. The report goes on to say that at-risk behaviors and shortcuts that do not immediately result in patient harm have the potential of becoming standard practice, escalating the odds that eventually someone will get hurt. The white paper lists the most common at-risk behaviors among healthcare professionals as:

• engaging in "grab and go" without fully reading the label of a medication before it is dispensed, administered or restocked;
• being intimidated or reluctant to ask for help or clarification;
• failing to educate patients;
• using medications without complete knowledge of the medication;
• failing to double-check high-alert medications before dispensing or administering; and
• failing to communicate important information (e.g., patient allergies, diagnosis/co-morbid conditions, weight, etc.).

While each situation where medication misuse occurs is unique, NCC MERP makes several recommendations to help practitioners establish an organizational culture that minimizes at-risk behavior among staff. These recommendations, titled *Reducing Medication Errors Associated with At-Risk Behaviors by Healthcare Professionals*, can be accessed on its website at www.nccmerp.org/council/council2007-06-08.html.

Systematic Safeguards: Using Bar Codes, Computerized Prescriptions and Other Methods to Improve Patient Safety

Leading hospitals across the country are already utilizing various programs to improve patient safety. A story published by ABC News and World News Tonight compiled information obtained from top hospitals to highlight some of their best practices and strategies:

- Electronic Tracking: Johns Hopkins Hospital in Baltimore, Md., uses electronic tracking of patient medications, called medical reconciliation, when patients are transferred from the intensive care unit (ICU) to another area of the hospital. If the medicine patients were given in the ICU does not match the medicine they receive in the new unit, the doctor is alerted of the error.
- Creating a Safe Culture: The Mayo Clinic in Rochester, Minn., has systems in place that encourage, support and reward the reporting of errors.
- E-Warnings: Cleveland Clinic has a system that warns doctors of possible drug interactions with other medications already taken by the patient when a new prescription is entered into the system.
- Smart Infusions: Massachusetts General Hospital in Boston uses smart infusion devices that have built-in drug libraries to ensure that patients are given the correct dosage of IV medication.
- Larger Lettering: UCLA Medical Center in Los Angeles found simply using a larger font on IV bag labels and patient wristbands makes it less likely that a nurse will give the patient an incorrect drug.
- X-Ray Technology: University of Michigan Hospitals and Health System in Ann Arbor, Mich., boasts a system called ValiMed that uses ultraviolet light to check the concentration and chemical makeup of IV solutions mixed by pharmacists, a process prone to error especially while dosing medications for kids.
- Bar Codes: Stanford Hospital and Clinics in California ensures all pill packages are barcoded, allowing nurses to match the barcode on a patient's wristband to that on the pill.
- Robotic Assistance: University of Pittsburgh Medical Center features a robotic arm in the pharmacy that sorts out the patients' pills. An actual robot then delivers the medications to the various floors.

FDA Launches Safe Use Initiative

Tens of millions of people in the United States depend on prescription and over-the-counter medications to maintain their health. Without a doubt, countless patients are helped by these medications. But there also are millions who are accidentally harmed by their improper use. To address this growing concern, the Food and Drug Administration (FDA) has launched a new program titled the Safe Use Initiative. The program is aimed at lowering the likelihood of preventable harm from the use of various medications. "Too many people suffer unnecessary injuries from avoidable medication misuse, errors and other problems," says FDA Commissioner Margaret A. Hamburg, MD. "The FDA is launching the Safe Use Initiative to develop targeted solutions for reducing these injuries."

Recognizing that collaboration is a key to the initiative's success, the FDA is reaching out to healthcare providers and other stakeholders to identify which drugs and drug classes are most often associated with preventable harm. The next steps in the initiative are slated to include a list of specific problems and the identification of cross-sector interventions for reducing harm. "Only through coordinated interventions across all sectors of the healthcare system can we substantially reduce preventable injuries from using medications," says Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research.

Meanwhile, the FDA has released new requirements for manufacturers of over-the-counter liquid products that are packaged with calibrated cups, droppers, syringes and spoons. According to the agency, some dosage-delivery devices are unclear or are inconsistent with the labeled dosing instructions. "Many accidental overdoses result from confusion about exactly how much of a drug to take. Better measuring devices will help patients, parents and other caregivers use the right amount of these medications ... especially for children," Woodcock adds.

Clearly, medication mistakes can occur at many junctures in the pharmaceutical supply chain for a variety of reasons.

The FDA initiative also proposes an evaluation of patient education materials on medications; communication about the risk of inadvertent overexposure to acetaminophen; putting safeguards in place to prevent surgery fires caused by alcohol-based surgical preps; and avoiding contamination of multiple-use medication vials. The FDA plans to work with the healthcare industry and the public as it develops new guidelines intended to prevent harm from medication use. ❖

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Shoring Up Supply Chain Security

As the saying goes, a chain is only as strong as its weakest link. From purchasing to storage and delivery, establishing supply chain integrity requires a closer look at best practices that put patient safety first.

By Trudie Mitschang

The pharmaceutical supply chain has long been vulnerable to counterfeit products, theft and price gouging. Preventing the infiltration of counterfeit pharmaceuticals into the legitimate pharmaceutical supply chain is an important public health issue that impacts patient welfare and healthcare costs. As a result, pharmaceutical firms are under scrutiny to shore up security measures and identify areas of increased vulnerability. But where are the weakest links?

Many supply chain problems are due to criminal counterfeit activity and theft — products being stolen from distributors and manufacturers and then resold in gray markets. But when it comes to patient safety, integrity of products as they make their way through the channel is also critical. Issues of storage, shipping and tracking come into play for companies hoping to achieve impeccable safety track records. This is especially true for

manufacturers and distributors of critical-care biopharmaceuticals, such as fragile plasma derivatives and other specialty products. When these life-sustaining products are compromised, tainted products can pose a serious health threat to patients on the receiving end. Of course, most patients are unaware of the inherent risks of a compromised pharmaceutical supply chain — until it touches them personally. Just ask Denise Hasenstab.

Hasenstab is a Mission Viejo, Calif., resident who suffers from a genetic gamma globulin deficiency and multiple sclerosis — chronic conditions that have severely compromised her immune system. Over a period of six years starting in 1998, she sought treatment for her illnesses at an infusion clinic near her home, receiving pricey, twice-weekly infusions of intravenous immune globulin (IVIG). Or so she thought. When it was discovered that Hasenstab's health had deteriorated, despite the costly care, the mother of two was shocked to learn her IVIG infusions had been tampered with; instead of life-sustaining immune globulin, she had been infused with a saline solution. Although Hasenstab has recovered from her ordeal and reached a settlement in a civil suit against the clinic, it hardly makes up for the trauma she endured.[1]

"There is no dollar amount I ever could have received that could even come close to making up those lost years of my life," she said. "Money can't bring back that time with my children. Those years are gone."

Re-examining Purchasing Options

Unlike other industries, pharmaceutical products are not necessarily shipped straight from the manufacturer to the customer. Often, they go through primary and sometimes secondary wholesalers to get to the customer. Within the supply chain, secondary wholesalers/distributors buy from the major drug wholesalers and each other, and then sell to the customer. According to Chris Ground, senior vice president national accounts, FFF Enterprises, distributors for plasma proteins and critical-care products historically are purchased not only from manufacturers, but also from hospitals and other distributors, leaving room for product tampering and mishandling. A lack of stringent regulations has made this an easy entry point for counterfeiting and other illegal activity.

To counter this, the Healthcare Distribution Management Association has developed a series of business practices for distributors to help address common safety concerns. One of the chief suggestions is that companies perform due diligence on wholesalers that they do business with, and verify that the wholesaler is an authorized distributor for the products in question. Another option suggested by members is for companies to deal only with manufacturers.[2] These suggestions have merit, and many leading companies are complying by making streamlined purchasing decisions. Genetech Inc., for example, currently requires distributors to certify that they will purchase the company's human growth hormone only from Genetech.[3] Amgen, Ortho Biotech, Serono, Johnson & Johnson, Pfizer and others have taken similar measures with specific products.

Creating Security, Link by Link

As the nation's largest distributor of plasma products, vaccines and critical-care biopharmaceuticals, FFF Enterprises is known as a leading voice when it comes to defining the components of supply chain safety. The company has implemented several best practices designed to put patient safety first, even coining the phrase "The Eight Critical Steps to Guaranteed Channel Integrity." The eight steps in FFF's safety protocol are increasingly becoming industry-recognized standards when it comes to moving products securely through the distribution channels.

"Each of the eight steps is critical and dependent on the others to make sure patient safety is not compromised," says Patrick M. Schmidt, founder and chief executive officer of FFF Enterprises, Inc. "It is our hope that these eight steps create a standard for safety that will continue to have a positive influence on the industry as a whole."

Interestingly, the first safeguard listed among FFF's eight recommendations is one also suggested by the Healthcare Distribution Management Association — that companies purchase products only from the manufacturer. Now in its 22nd counterfeit-free year, FFF also has made the key business decision to sell to only certified healthcare providers.

Most patients are unaware of the inherent risks of a compromised pharmaceutical supply chain — until it touches them personally.

Another critical step that plays an important role in pharmaceutical supply chain safety pertains to storage issues. Many pharmaceutical products are highly sensitive to temperature variations and storage facility conditions, which is why storage and transporting conditions must be tightly controlled using stringent guidelines. Best practices for distribution sites include the use of temperature-controlled warehouses with state-of-the-art monitoring systems and adequate backup generators. Stacking methods also can be modified in storage units to avoid putting pressure on fragile bottles and containers.

Product packaging is another key safety link, an especially

important component for frozen or refrigerated products. While this link seems obvious, it is important to distinguish each step to see how one depends on another. Analyzing specific requirements of each product during packaging ensures that integrity is maintained during transit. Quality packaging standards may include insulation between products, gel fillers and temp tails to indicate whether a product gets too hot or too cold during shipping.

In the pharmaceuticals distribution business, another critical step relates to product allocations to customers, which are naturally based on supply and demand. But in volatile markets, product shortages or inventory overages can create issues for patients and providers. When possible, taking a more interactive approach to allocation based on immediate rather than long-term customer needs can help create balance and minimize distribution disruptions. "Helping healthcare care is about getting products to patients when they need it, while creating a secure supply chain that is resistant to gray market tampering," explains Ground.

Unlike other industries, pharmaceutical products are not necessarily shipped straight from the manufacturer to the customer.

Delivery guidelines and methods are also important factors. Extreme weather and storms can — and should — impact shipping methods and protocols. Overnight shipping of critical-care products during times of extreme weather can ensure efficacy is maintained and that products are delivered when and where patients need them most. Another important factor can be the decision to not deliver to unlicensed facilities.

"Our own delivery guidelines are in compliance with the State Board of Pharmacy requirements. The types of products we deliver must only be transported to facilities with a DEA [Drug Enforcement Administration] license, no exceptions," adds Ground.

Verification and tracking comprise the final links in supply chain safety. The ability to verify a product's pedigree and trace exactly where it has been is critical. Companies like FFF use advanced technology to help customers take charge of shipments. FFF's system, called Verified Electronic Pedigree (VEP), allows customers to easily verify the pedigree of purchased pharmaceuticals within seconds of logging into the company's computerized system. Electronic tracking also is a helpful reassurance, matching product lot numbers to customer information. Another important safeguard involves having a dedicated workforce to monitor manufacturer and U.S. Food and Drug Administration information sources, ensuring the timely communication of important product safety or recall notices.

Prioritizing Patient Safety

Increasing awareness is always the first step to implementing change in any segment of business. A study conducted by Marsh's Supply Chain Risk Management Practice, in conjunction with *Pharmaceutical Manufacturing* magazine, surveyed representatives from 66 leading life sciences organizations, and results suggested that the globalization of the industry has, in fact, undermined the security of an already vulnerable supply chain. The study went on to say that pharmaceutical manufacturers may have significantly less control over supply chain security than they think.

The report recommended that companies can contribute to supply chain safety by building in processes, standards, policies and procedures that work together to close gaps and strengthen weak links. Re-evaluating systems and best practices, while taking a closer look at each individual supply chain link, is a good first step.[4]

Mitigating the risk of counterfeit and compromised pharmaceuticals will require the creation of a pharmaceutical supply chain that is both secure and resilient. Closing security gaps and strengthening weak links will demand multilayered measures and industry-wide developments of effective partnerships. A place to begin is by seeing the bigger picture — putting patient safety first. Safeguarding the integrity of pharmaceuticals and their distribution is not only a matter of brand equity, fiscal responsibility and corporate reputation, but in some cases, a matter of life and death for patients on the receiving end.

"One of the driving values behind everything we do at FFF is that patients are always first," Schmidt explains. "It's part of our culture to recognize that at the end of every transaction, there's a patient waiting for that product." ❖

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Important Safety Information

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

Hizentra is contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin preparations or components of Hizentra, such as polysorbate 80. Because it contains the stabilizer L-proline, Hizentra is contraindicated in patients with hyperprolinemia. Hizentra is also contraindicated in patients with immunoglobulin A deficiency who have known antibody against IgA and a history of hypersensitivity.

All IgA-deficient patients with anti-IgA antibodies are at greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. If hypersensitivity occurs or anaphylactic reactions are suspected, discontinue administration immediately and treat as medically appropriate.

Hizentra 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.

The most common drug-related adverse reactions (observed in 5% or more of subjects in the clinical trial) were local reactions (ie, swelling, redness, heat, pain, and itching at the injection site), headache, vomiting, pain, and fatigue.

Monitor patients for reactions reported to occur with IVIg treatment that might also occur with Hizentra, including renal dysfunction/failure, thrombotic events, aseptic meningitis syndrome (AMS), hemolysis, and transfusion-related acute lung injury (TRALI).

Ig administration can transiently impair the efficacy of live attenuated virus vaccines, such as measles, mumps and rubella. It can also lead to misinterpretation of serologic testing.

No overall differences in safety or efficacy were observed in patients over 65 or in pediatric patients. In the clinical study, desired serum IgG levels were achieved in pediatric patients without pediatric-specific dose requirements.

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

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

*Primary immunodeficiency disease.
†Subcutaneous immunoglobulin.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

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

5.2 Reactions Reported to Occur With IGIV Treatment

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

Renal Dysfunction/Failure

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

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

Thrombotic Events

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

Aseptic Meningitis Syndrome (AMS)

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

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

Hemolysis

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

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

Transfusion-Related Acute Lung Injury (TRALI)

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

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

5.3 Transmissible Infectious Agents

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

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

5.4 Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

Table 2: (Continued)

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

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

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

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

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

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

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

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

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

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

7.2 Serological Testing

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Hizentra has not been evaluated in nursing mothers.

8.4 Pediatric Use

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

Hizentra was not evaluated in neonates or infants.

8.5 Geriatric Use

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

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STAMP OF APPROVAL

H1N1 and the Flu Vaccine Licensing Process

By Amy Scanlin, MS

The extensive process through which the FDA approved the 2009 H1N1 flu vaccine mirrors what is required for the licensure of seasonal flu vaccines.

As reports of the "new" 2009 H1N1 (swine) flu emerged last spring, its unknown implications frightened many. But, even more frightening was the fact that there was no vaccine to prevent it. And, it appeared highly likely that, considering the time required to get a vaccine to market, it would not be ready when the first wave of the 2009 H1N1 flu hit. Yet, while it was in short supply during that first wave, vaccine did become available, despite the many steps required to obtain approval by the Food and Drug Administration (FDA).

Of course, the speed needed to get the 2009 H1N1 vaccine into circulation to inoculate tens of millions of Americans raised concerns about its safety. And, when the first doses of the vaccine were distributed in the U.S. in October, a mere five months after 2009 H1N1 came on the scene, many were skeptical of the approval process. But, the scrutiny the 2009 H1N1 vaccine underwent for approval was at least equal to, if not more intensive than, the annual review of the seasonal flu vaccine. Understanding how the approval process works may help to alleviate both physicians' and patients' concerns.

Determining a Virus' Strain

When the World Health Organization (WHO) declared the 2009 H1N1 flu virus a pandemic last June, an incident management system was used by staff at the FDA to look at the virus and determine the appropriate response. According to FDA Public Affairs Specialist Paul Richards, "Scientists immediately began working with WHO Essential Reference Laboratories (ERL) to make a reference strain for possible use in vaccine production and to prepare potency testing reagents to be used in the development of seed viruses needed for vaccine formulation. Additionally, a pathway to approval was developed and presented to the public on July 23, 2009, during a meeting with the Vaccines and Related Biological Products Advisory Committee (VRBPAC).

Prior to this time, experts from the FDA, WHO, the Centers for Disease Control and Prevention (CDC) and other institutions were studying virus samples and patterns collected from around the world in an effort to identify strains that were most likely to cause the most illness in the upcoming season. Based on those forecasts and on the recommendations of VRBPAC, the FDA determined the strains that manufacturers should include in their vaccines for the U.S. population. Unfortunately, by the time the 2009 H1N1 strain had been identified, it was too late to include it in the seasonal flu vaccine for this season, so it became its own vaccination.[1]

As such, the 2009 H1N1 vaccine was approved as a strain change to each manufacturer's FDA-approved seasonal influenza vaccine. And, shortly after the VRBPAC meeting, the FDA began receiving strain change supplements, with the first four approved in September.

The Process of Vaccine Production

The 2009 H1N1 vaccine was approved and evaluated by the FDA after review of supplemental applications submitted by manufacturers, using the same regulatory process by which it approves new viral strains contained in the annual seasonal influenza vaccines. And, while these strain change supplements are not required to be supported by new clinical data, immunogenicity and safety data were made available through clinical studies.

After production, the vaccine underwent testing in clinical trials by several thousand volunteers, which took place in three phases. First, there were safety studies on a limited number of people. Next, there were studies of dosage amounts conducted on hundreds of people. And, last, thousands of trials were conducted on people taking the vaccine so scientists could study its effectiveness, safety and side effects.

The speed needed to get the H1N1 vaccine into circulation to inoculate tens of millions of Americans raised concerns about safety.

When all three phases were successfully underway, the manufacturers received the approval from the FDA for the request to supplement their Biologics License Application (BLA) for influenza virus vaccine to include the new influenza (H1N1) 2009 monovalent vaccine. At the same time, the FDA acknowledged the manufacturers' commitments to submit results from ongoing clinical studies, which would be used as an efficacy supplement to the existing BLA.[2]

Safety First

Because less than half of the expected 2009 H1N1 vaccine doses had been delivered by early December, many called the vaccine production method into question. The current method relies on egg-based technology, which requires growing cultures in hundreds of millions of eggs to create vaccines. Unfortunately, using this method, there is no way to speed up the process. (New production methods are now being tested. See the article, "Scientists Flying the Coop on Flu Vaccine Manufacturing," on page 48 of the January 2010 issue of *BioSupply Trends Quarterly*.) This slow pace of 2009 H1N1

vaccine delivery prompted Health and Human Services secretary Kathleen Sebelius to call for a federal review of the handling of public health emergency preparedness.

But, safety must come before efficiency. According to Richards, "Although there were tremendous efforts to get a vaccine on the market as quickly as possible, the vaccines approved for this pandemic were approved and manufactured with the same production and testing methods used in the seasonal vaccines. These methods and tests were previously approved at the time each manufacturer was initially licensed to manufacture influenza vaccines, and are based on decades of influenza vaccine experience and a strong scientific foundation. Protecting the public health is [the] FDA's primary mission. Emergency preparedness is an important part of that effort."

Monitoring for Safety

Once a vaccine is on the market, many different organizations monitor it for safety. The FDA and CDC oversee its production and safety through the CDC's Immunization Safety Office (ISO) using a number of methods, including the Vaccine Adverse Event Reporting System (VAERS), which looks for adverse events or side effects either coincidental or attributed to the vaccine that might be significant to public health. With VAERS, physicians, clinicians and even family members or the patients themselves can voluntarily report any adverse or suspected adverse effects after a patient receives a vaccine. The FDA and CDC cannot determine from this report whether there is a clinically significant link between the adverse effect and vaccine, but it can refer those cases that warrant further investigation.[3]

When the World Health Organization (WHO) declared the H1N1 flu virus a pandemic last June, an incident management system was used by staff at the FDA to look at the virus and determine the appropriate response.

VAERS can be thought of as an "early warning detection."

The Vaccine Safety Datalink (VSD) project is a collaboration between the FDA and eight managed care organizations that review adverse events that could be associated with new vaccines via a large linked database.[4] Established in 1990, the VSD looks at the date of the vaccination, the type of vaccine and other metadata, and can compare results to millions of other patients to determine safety outcomes.

The Clinical Immunization Safety Assessment (CISA) Network, made up of six medical research centers with expertise in immunization safety, meets monthly to look at specific adverse event cases to determine an assessment of the situation and a plan.[5] And, the Center for Biologics Evaluation and Research (CBER) within the FDA regulates vaccine products once they are approved and coordinates the availability of those vaccines.

Should a vaccine or vaccine batch need to be recalled, typically it is due to its effectiveness, rather than its safety. When vaccine potency is discovered to be weakened, the ensuing recall usually is voluntary on the part of the manufacturer. This was the case when Sanofi Pasteur determined that four lots, or about 800,000 doses, of its pediatric prefilled syringes of 2009 H1N1 vaccine had a drop in its potency (strength) below the required range.[6] Similarly, MedImmune reported 13 batches of its nasal spray vaccine had lost potency.[7] Both companies notified the FDA and CDC, and the lots were recalled.

Rare Side Effect

Some skeptics are still questioning the 2009 H1N1 vaccine safety. One reason is the potential for the rare occurrence of

Guillain-Barré syndrome (GBS), which was reported in 1976 after the introduction of another swine flu vaccine. The WHO calls the relationship between GBS and the 1976 vaccine "well established" and "causal."[8]

That vaccine was suspended when it was apparent that the risk of developing GBS slightly increased with its use. According to the CDC, GBS normally strikes one to two out of 100,000 people, while the 1976 swine flu vaccine was associated with GBS at a rate of one additional case per 100,000 people. And, while subsequent studies of seasonal flu vaccines have shown no consistent relationship between the vaccine and the incidence of GBS,[9] two studies did find a potential link between the seasonal flu vaccine and a slight increase in GBS risk.[10]

According to the VAERS report for Jan. 8, 2010, 37 cases of GBS are under investigation in the U.S.[11] (In the U.S., approximately 80 to 160 GBS cases are expected each week, regardless of vaccinations.)

Monitoring = Patient Safety

States are now able to offer the 2009 H1N1 vaccine to all residents, not just high-risk groups. And, the FDA, CDC and other local, state and federal organizations continue to monitor its safety. At the same time, manufacturers are analyzing their production methods and vaccine potency. Couple this with maintaining strict FDA approval processes for vaccines — even in times of crisis — and it's clear that many organizations are working responsibly to keep our population safe and to keep the 2009 H1N1 virus at bay.

In the 2010-2011 influenza season, manufacturers will look to re-create this mirrored process and produce new virus strains to be included in the season's flu vaccine. And, because the H1N1 virus likely will once again pose a serious threat, it will be combined with two other strains in time for the next season's trivalent flu vaccine. ❖

Once a vaccine is on the market, many different organizations monitor it for safety.

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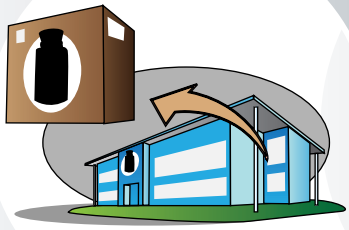

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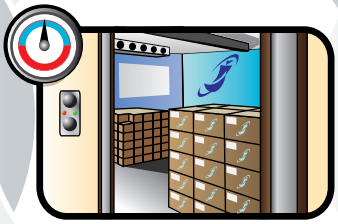

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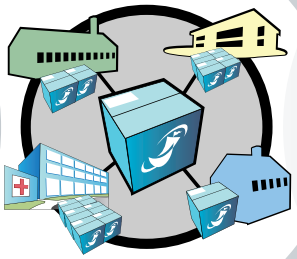

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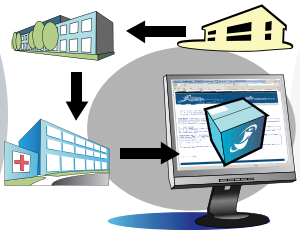

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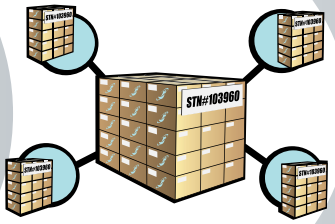

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Counteracting the Anti-Vaccine Movement: Promoting an Ounce of Prevention

By Trudie Mitschang

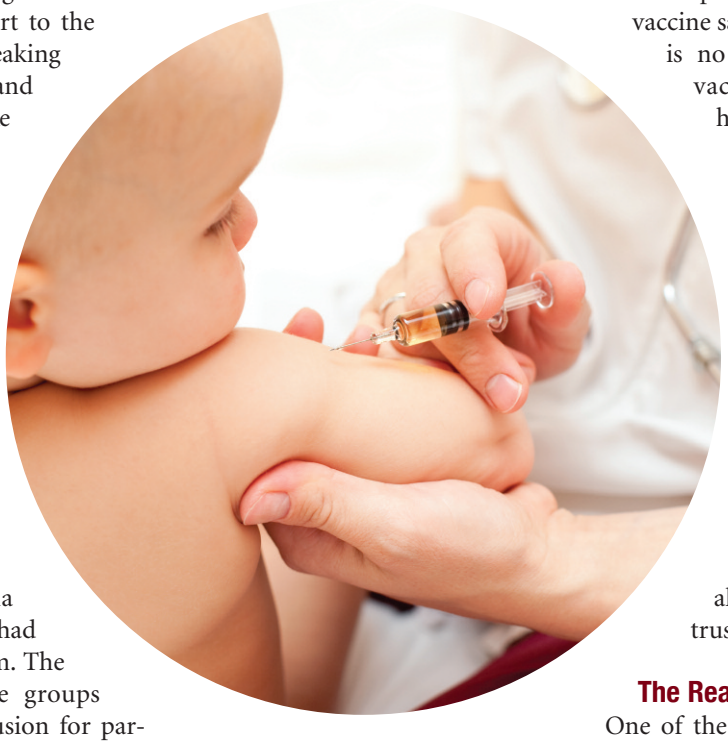
Providers hoping to counteract the anti-vaccine movement can cultivate trust by setting aside time for vaccine discussions and using effective, empathetic communication to encourage vaccine compliance.

Over the past decade, perceptions and concerns about vaccine safety have steadily increased vaccine refusal rates in the United States. Currently, several states allow for "personal belief" exemptions from school vaccination requirements, in addition to exemptions for religious or medical reasons. What is the cause for concerns about vaccines, and how can healthcare providers overcome them?

Vaccines and Autism

The rise in parental resistance to once-routine vaccinations is, in many cases, directly tied to concerns linking vaccines to rising instances of childhood autism. This theory first gained ground in 1998 after a study was published in the British medical journal *The Lancet*, despite an editorial published in the same issue that discussed concerns about the validity of the study, the dismissal of the study by medical professionals, as well as a host of new research. Since then, what has been dubbed the "anti-vaccine movement" has garnered increased attention and momentum, and several scientific studies have debunked the connection between thimerosal, a mercury-based preservative that was once used in most vaccines, and autism. Vaccine opponents believe this ingredient has helped trigger the growing number of autism cases and other neurological disorders in vaccinated children.

Clinicians hoping to educate the public, particularly parents, about the safety and benefits of vaccines have faced an uphill battle. In recent years, celebrity parents whose own children have been diagnosed with autism have lent their support to the anti-vaccine movement by speaking out on national talk shows and using social media tools, like blogs, Facebook and Twitter, to get their messages out. This increased media focus has helped catapult the anti-vaccine movement from a somewhat fringe discussion to a mainstream debate, with heated opinions on both sides.



Another setback for healthcare providers occurred in March 2008 when the U.S. government awarded compensation to a Georgia family that claimed vaccines had caused their daughter's autism. The decision rallied anti-vaccine groups and created even more confusion for parents grappling with questions about the safety of vaccinations.

Recent events may help to turn the table on the battle. Last year, reports surfaced that the author of the study that was published in *The Lancet*, Dr. Andrew Wakefield, may have altered data after being paid $1 million to examine autistic children whose parents blamed the measles, mumps, rubella (MMR) vaccine for the illness. Then, this past February, that same article highlighting this study was retracted by the editor of the journal just days after the United Kingdom's General Medical Council ruled that Dr. Wakefield acted improperly during his research. According to a statement by the Centers for Disease Control and Prevention (CDC), *The Lancet*'s decision to retract the article "builds on the overwhelming body of research by the world's leading scientists that concludes there is no link between MMR vaccine and autism. We want to remind parents that vaccines are very safe and effective, and they save lives. Parents who have questions about the safety of vaccines should talk to their pediatrician or their child's healthcare provider."

Unfortunately, anecdotal information and Internet-gleaned research seems to resonate louder than physician opinion for parents who remain on the fence. These days, it seems many in the medical community are viewed with increasing skepticism.

"I've spoken to my pediatrician about vaccine safety, and she assures me there is no proven correlation between vaccinations and autism. But how can I ignore people who noticed a change in their child after vaccination?" asks April Jace, a Los Angeles school teacher and mother of three. "My older boys have had all their vaccinations, but so far I have not scheduled my 14-month-old for his recommended 15-month shots. I have to wait until I read more and get more educated about it. I don't want to be paranoid, but I also don't want to just blindly trust my pediatrician either."

The Reality of Time Constraints

One of the challenges physicians face in adequately addressing parental concerns regarding vaccines is a practical one: With a busy caseload of both well-child visits and sick children who need immediate attention, pediatricians are often thrown off guard when hit with a list of vaccine questions that they may not be prepared to answer. Dr. Bob Sears, pediatrician and author of *The Vaccine Book*,

says he has made it a policy not to discuss vaccine safety during regular checkups, preferring to schedule a separate consultation for parents who have a lot of unanswered questions.

"When you have about 15 minutes to complete a regular checkup and a parent hits you with 20 minutes' worth of questions about vaccines, there is simply no way to adequately address their concerns," he explains. "I've found that scheduling a separate vaccine consultation allows for a much more focused and, hopefully, informative discussion. That way I'm not frustrated by time constraints, and the parent has my undivided attention. This is an emotional issue for many people, and it's important that they feel as if they've been heard."

According to the CDC website, effective, empathetic communication is critical in responding to parents who are considering not vaccinating their children. And, it says, "parents should be helped to feel comfortable voicing any concerns or questions they have about vaccination, and providers should be prepared to listen and respond effectively."

Clinicians hoping to educate the public, particularly parents, about the safety and benefits of vaccines have faced an uphill battle.

Promoting Community Immunity

The debate over vaccine safety is a polarizing one, pitting parent against parent, patient against physician, and leaving vaccine manufacturers and administrators caught in the middle. For some, refusing to vaccinate a child is a personal decision that should not come under scrutiny by anyone outside of the immediate family. But vaccine proponents argue that a decision against immunization puts entire communities at risk. In reality, even children whose parents do not refuse vaccination can be put at risk because

Best-Practice Tips for Communicating with Vaccine-Resistant Parents

The Centers for Disease Control and Prevention (CDC) suggests using the following guidelines during vaccine consultations:

- Evaluate whether the child has a valid contraindication to a vaccine by asking about medical history, allergies and previous experiences.
- Assess the parents' reasons for wanting to delay or forgo vaccination in a non-confrontational manner. (Have they had a bad experience? Obtained troubling information? Do they have religious or philosophical reservations?)
- If parents have safety concerns or misconceptions about vaccination, ask them to identify the source(s) of those concerns or beliefs.
- Listen carefully, paraphrase to the parents what they have told you, and ask them if you have correctly interpreted what they have said.
- Provide factual information in understandable language that addresses the specific concerns or misconceptions the parents have about vaccination.
- Use Vaccine Information Statements (VIS) for discussing vaccine benefits and risks. Before administering each dose of certain vaccines, providers are required by law to give a copy of the current VIS to the child's parent/legal guardian. Providers must also record in the child's chart the date that the VIS was given and the publication date of the VIS. The updated versions of VIS can be found at www.cdc.gov/vaccines/pubs/VIS/.

  VIS in a variety of languages can be obtained at www.immunize.org/vis/.
- Educate parents about the dangers of vaccine-preventable diseases and the risks of not vaccinating as they relate to the child, family and community.
- Express your personal support for vaccinations, and share experiences you have had with children with vaccine-preventable diseases.
- Provide educational materials to be taken home, and refer the parent to other credible sources of information such as CDC's National Immunization Information Hotline or website.

"community immunity" normally protects children who are too young to be vaccinated, who can't be vaccinated for medical reasons, or whose immune systems do not respond sufficiently to vaccination. When higher numbers of people go unvaccinated, once-obscure diseases like measles and whooping cough begin making a comeback, and for the most vulnerable members of society, the consequences can be deadly.

To achieve community immunity, more than 95 percent of a community would need immunization, which means childhood vaccinations need to go from being viewed as a personal

Best-Practice Tips for Communicating with Vaccine-Resistant Parents

With the recent retraction of an article that appeared in the February 1998 British medical journal *The Lancet*, there are no proven data to suggest that the measles, mumps, rubella (MMR) vaccine will increase the risk of developing autism or any other behavioral disorder. However, there is plenty of scientific research to suggest that there is no causal association at all.

This research begins with the study reported on in *The Lancet*, which was based on data from 12 patients. Dr. Andrew Wakefield and colleagues speculated that MMR vaccine may have been the possible cause of bowel problems that led to a decreased absorption of essential vitamins and nutrients that resulted in developmental disorders like autism. However, no scientific analyses were reported to substantiate the theory. For instance, there is no clinical data that support the theory that autism may be caused by poor absorption of nutrients due to bowel inflammation. Plus, in at least four of the 12 cases in the study, behavioral problems appeared before the onset of symptoms of inflammatory bowel disease. What's more, Dr. Wakefield and his colleagues later published another study in which highly specific laboratory assays in patients with inflammatory bowel disease were negative for measles virus.

In an investigation conducted in 1999 by a Working Party on MMR Vaccine of the United Kingdom's Committee on Safety of Medicines, several hundred reports of autism, Crohn's disease or similar disorders developing after receipt of MMR or MR vaccines were evaluated. The Working Party concluded that the results of their investigation did not support the suggested causal associations or give cause for concern about the safety of MMR or MR vaccines. The American Medical Association has since reached the same conclusion.

In a study conducted in certain districts in London, England, researchers investigated 498 known cases of autism spectrum disorders (ASD), which includes classical autism, atypical autism and Asperger's syndrome, born in 1979 or later and linked to an independent regional vaccination registry. They found that while the known number of ASD cases has been increasing since 1979, there was no jump after the introduction of MMR vaccine in 1988. Those vaccinated before 18 months of age had similar ages at diagnosis as did cases who had been vaccinated after 18 months or not vaccinated. At 2 years old, the MMR vaccination coverage among ASD cases was nearly identical to coverage in children in the same birth cohorts in the whole region. Further, the first diagnosis of autism or initial signs of behavioral regression were not more likely to occur within time periods following vaccination than during other time periods.

Between January 1990 and February 1998, only 15 cases of autism behavior disorder after immunization were reported to the Vaccine Adverse Events Reporting System (VAERS), and it was determined that because of the small number of reports, the cases reported are likely to represent unrelated chance occurrences that happened around the time of vaccination.

In 2000, the American Academy of Pediatrics convened a multidisciplinary panel of experts to review what is known about the development, epidemiology and genetics of ASD and the hypothesized associations with IBD, measles and MMR vaccine. The panel concluded that the available evidence does not support the hypothesis. And, recently, the National Childhood Encephalopathy Study was examined to see if there was any link between measles vaccine and neurological events. The researchers found no indication that measles vaccine contributes to the development of educational and behavioral deficits or other possible signs of long-term neurological damage.

The Centers for Disease Control and Prevention (CDC), Federal Drug Administration, National Institutes of Health and other federal agencies continue to routinely examine any new evidence that suggests possible problems with the safety of vaccines. Currently, the CDC is conducting a study in the metropolitan Atlanta area to further evaluate any possible association between MMR vaccination and autism.

Vaccine proponents argue that a decision against immunization puts entire communities at risk.

decision to more of a larger social obligation. This moral consideration is a missing component in many discussions between physicians and parents, but it's an important one. The CDC stresses that education is key when it comes to achieving vaccine compliance, and encourages physicians to inform parents who defer vaccination of their responsibilities to protect other family and community members, including people who may be immunocompromised. The CDC also suggests parents be advised of state school or childcare entry laws that might require that unimmunized children stay home from school during outbreaks of vaccine-preventable diseases.

In an article published in the *New England Journal of Medicine*, lead author Saad B. Omer, MBBS, PhD, MPH, assistant professor of global health and epidemiology at Emory University's Rollins School of Public Health, reviewed evidence from several states that vaccine refusal puts children at substantially higher risk for infectious diseases such as measles and pertussis. Omer stated, "The implication of recent research findings is that everyone who is living in a community with a high proportion of unvaccinated individuals has an elevated risk."

Understanding Risk Communication

Few of today's parents can recall the devastation of diseases such as smallpox, mumps or polio, which makes communicating the value of vaccines a difficult prospect for physicians. Educating parents about the risks of such diseases is important, but equally important is the need to honestly address perceived vaccine risks. A workshop on risk communication and vaccination sponsored by the Institute of Medicine's Vaccine Safety Forum covered various discussion dynamics between the general public and healthcare providers. Among the findings:

• Effective risk communication depends on the providers' and recipients' understanding, more than simply the risks and benefits; background experiences and values also influence the process and outcome.

• The goal that all parties share regarding vaccine risk communication should be informed decision-making. Consent for vaccination is truly "informed" when members of the public know the risks and benefits and make voluntary decisions.

• Trust is a key component of the exchange of information at every level, and overconfidence about risk estimates that are later shown to be incorrect contributes to a breakdown of trust among public health officials, vaccine manufacturers and the public.

Several resources are available to assist healthcare providers in addressing the benefits and risks of vaccination. Federal law requires all healthcare providers who administer vaccines in the United States to provide Vaccine Information Statements (VIS) to vaccine recipients (or their parent or guardian) prior to each dose. VIS are developed by the CDC and contain information on the disease, as well as the risks and benefits associated with immunization. Since the technical and medical language in these statements can sometimes be difficult for lay people to understand, discussing the information contained in the VIS with the parent/patient is also an excellent way to bridge the communication gap and encourage the administration of scheduled vaccines. ❖

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

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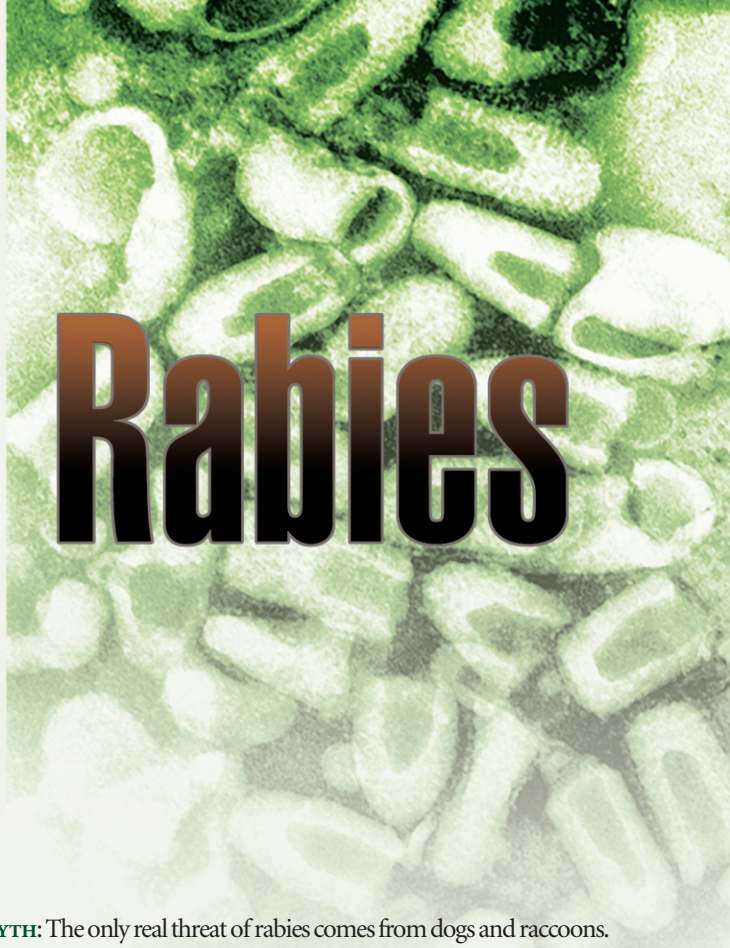

Myths and Facts: Rabies

Rabies is a viral infection that is easily preventable, but almost always fatal if not treated.

By Ronale Tucker Rhodes, MS

More than 55,000 people worldwide die of rabies each year, with 95 percent of the fatalities occurring in Asia and Africa.[1] Fortunately, due to improved control and vaccination of domestic animals, as well as the development of effective post-exposure treatment and vaccines, the number of rabies-related deaths in the United States has declined over the past century from 100 annually to just one or two each year.[2] But, while the rate of rabies deaths has dropped dramatically, the rate of rabies infection is no less of a concern. Thousands of people are still exposed to the rabies virus, and many of those people fail to seek medical attention, mainly because they are unaware of their exposure, but also because they are misinformed. Understanding the facts about how they can contract rabies and how to prevent infection is essential.

Myth: Rabies is not a major concern in the U.S.

Fact: Rabies has been reported in every state except Hawaii. In 2006, 49 states, the District of Columbia and Puerto Rico reported 6,940 cases of rabies in animals and three human cases to the Centers for Disease Control and Prevention. The total number of reported cases increased by 8.2 percent from those reported in 2005 (6,418 cases). Although human deaths from rabies are now rare in the U.S., every year approximately 40,000 persons receive postexposure treatment for rabies exposure.[3]

Myth: Rabies can only be transmitted by a rabid animal bite.

Fact: Rabies can be transmitted through a wound, scratch or other break in the skin if it comes in contact with the animal's saliva.[4] Very rarely, rabies has been transmitted without an actual bite.[5]

Myth: The only real threat of rabies comes from dogs and raccoons.

Fact: While dog bites continue to be a common cause of rabies in developing countries, wild animals are the most common cause of rabies in developed countries.[1] Domestic animals account for less than 10 percent of the reported rabies cases, with cats, cattle and dogs most often reported rabid.[2] However, there have been no reports of rabies caused by dog bites in the U.S. for many years due to widespread animal vaccination. What is more frequently reported now is rabies caused by bats and raccoons.[5] Other wild animals that carry the rabies virus are wild foxes, skunks, jackals and wolves, although transmission from these animals is rare. In addition, livestock, horses and deer can become infected with rabies, and although they could transmit the virus to other animals or people, this rarely occurs.[1]

Myth: Rabid animals will always froth at the mouth.

Fact: Although foaming at the mouth is a sign of rabies, it is also a symptom of more common ailments, including distemper, ticks, diabetes, liver failure, allergies and dehydration. And since it is not always characteristic of rabies, it should never be assumed that because an animal is not foaming at the mouth that it doesn't have rabies.[6]

Myth: Rabid animals are afraid of the water.

Fact: Humans infected with rabies suffer painful muscle spasms while attempting to swallow, which can cause a fear of water. However, rabid animals are not afflicted with these spasms and, thus, can drink as much water as they want.[4]

Myth: After coming into contact with a suspected rabid animal, an individual should never try to capture it.

Fact: When humans are exposed to suspected rabid animals,

attempts to identify, capture or humanely sacrifice the animal should be undertaken immediately. In addition, post-exposure treatment should begin right away and only be stopped if the animal is a dog or cat that remains healthy after 10 days. Animals that have been sacrificed or that have died should be tested for rabies.[1] Immunofluorescence microscopy, the most rapid and accurate test method, looks at the brain tissue after an animal is dead to diagnose rabies. A similar test checks for rabies in humans, using a piece of skin from the neck. And, doctors may also look for the rabies virus in humans in their saliva or spinal fluid.[5]

Myth: First aid won't help a person who has been infected by a rabid animal.

Fact: Cleansing wounds and getting immunized against rabies immediately after contact with a suspected animal can prevent the onset of rabies in 100 percent of exposures. If individuals have merely touched or fed an animal they suspect of having rabies, but their skin is still intact, it is recommended they clean and disinfect the point of contact. Individuals who have minor scratches without bleeding from contact, licks on broken skin, bites or other contact that breaks the skin also should have an anti-rabies immunization. In addition, an anti-rabies immunoglobulin (a blood product that contains antibodies against rabies) should be given to those who have bites, scratches, licks on broken skin, other broken skin contact or even exposure to bats, as well as to those who have weaker immune systems.[1]

Myth: Rabies is not necessarily fatal in humans.

Fact: Once symptoms of the disease develop, there is no cure. The virus infects the central nervous system, causing encephalopathy and, ultimately, death. Early symptoms are nonspecific, and consist of fever, headache and general malaise. As the disease progresses, neurological symptoms appear and may include insomnia, anxiety, confusion, slight or partial paralysis, excitation, hallucinations, agitation, hypersalivation, difficulty swallowing and hydrophobia (fear of water). Death usually occurs within days of the onset of symptoms.[2]

Myth: Rabies is always fatal.

Fact: Rabies is fatal if not treated quickly. However, if treated with vaccinations within 24 to 48 hours, rabies is rarely fatal to humans or animals.[6] In fact, vaccinations can prevent the onset of rabies in virtually 100 percent of exposures.[1]

Currently, there are two rabies vaccines: Imovax, manufactured by Sanofi Pasteur; and Rabavert, manufactured by Novartis Vaccines. While these vaccines are prepared in different ways, both are made from inactivated virus, and both are considered equally safe and effective. Treatment with these vaccines is known as post-exposure prophylaxis (PEP). An exposed person who has never received any rabies vaccine will first receive a dose of rabies immune globulin, which gives immediate, short-term protection. This shot should be given in or near the wound area. Follow-up care includes a series of rabies vaccinations. The first dose should be given as soon as possible after the exposure, with additional doses administered on days three, seven and 14 after the first shot. Anyone who has previously been given the rabies vaccine should receive two more doses — one dose immediately and one three days later. These shots should be given in the deltoid muscle of the arm. However, children also can receive the shots in the muscle of the thigh.[3]

Myth: Rabies shots are extremely painful.

Fact: In the past, rabies treatment was extremely painful because it involved multiple nerve-tissue-based vaccinations into the abdomen with a large needle. Now, however, the procedure involves fewer injections with a much smaller needle into the deltoid muscle of the arm.[7] The rabies vaccine today is no more painful than any other type of vaccination. ❖

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

Flebogamma® 5% DIF

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

(1) Mean value from 97 consecutive lots, data on file, Instituto Grifols, S.A.
(2) Berger M et al. A Multicenter, Prospective, Open Label, Historically Controlled Clinical Trial to Evaluate Efficacy and Safety in Primary Immunodeficiency Diseases (PID) Patients of Flebogamma 5% DIF, the Next Generation of Flebogamma. J Clin 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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FDA 03-1-US-09

GRIFOLS

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

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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

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

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

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

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

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

WARNINGS
Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Flebogamma® 5% DIF does not contain sucrose.
See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Flebogamma® 5% DIF is made from human plasma. As with all plasma derived products, the risk of transmission of infectious agents, including viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated. The risk that such products will transmit an infectious agent has been greatly reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Biologicals at 888-GRIFOLS (888-474-3657).
All patients, but especially individuals receiving Flebogamma® 5% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at risk for the development of inflammatory reactions characterized by fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations may reduce the risk of these types of events.

Appropriate supportive care, including immediate access to epinephrine injection, should be available for the management of acute anaphylactic reactions.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Respiratory	Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular	Cardiac arrest, thromboembolism, vascular collapse, hypotension
Neurological	Coma, loss of consciousness, seizures, tremor
Integumentary	Stevens-Johnson Syndrome, epidermolysis, erythema multiformae, bullous dermatitis
Hematologic	Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
General/Body as a Whole	Pyrexia, rigors
Musculoskeletal	Back pain
Gastrointestinal	Hepatic dysfunction, abdominal pain

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

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

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

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

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

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

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

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

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

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

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

Reported adverse reactions with Flebogamma® 5% DIF and other IGIV products include: headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema, often beginning within 60 minutes of the start of the infusion.
Rarely, Immune Globulin Intravenous (Human) can induce a severe fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with IGIV. In the case of shock, the current standard medical treatment for shock should be implemented.

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Our Excellent Biologics Safety Record: It's No Accident

by KEITH BERMAN, MPH, MBA

LAST YEAR, 30 domestic and overseas manufacturers distributed some 140 different plasma-derived therapeutics and vaccines for human use to U.S. hospitals, clinics, pharmacies and homecare providers. Thousands of batches and hundreds of millions of doses of vaccines, immunoglobulins, coagulation products, topical hemostasis agents, blood volume expanders and a host of other products were infused, injected or delivered by spray applicator.

Yet, throughout 2009, the Food and Drug Administration (FDA) reported just three product recall actions, which involved an anti-pneumococcal vaccine and a few batches of 2009 H1NI influenza vaccine. None involved any safety risk to patients. And in each instance, the FDA determined that the implicated lots were sufficiently potent, making it unnecessary even to revaccinate any patients.

That extraordinary 2009 safety record was no fluke. During the previous five years, from 2004 through 2008, the FDA reported an average of just three limited biotherapeutics recall actions a year. And, only three of those 15 recalls involved adverse clinical events; all were transient, non-life-threatening allergic reactions.

How can an industry that makes most of its products from human plasma and live viruses supply so many therapies at such volumes with this record of quality and safety?

It Starts with the Raw Material

No products approved for human use are subjected to more regulatory oversight than biologics. And, none receive more FDA scrutiny than those sourced from human or animal blood.

The FDA regulates these products under the authority of not one, but two laws: the Public Health Service Act and — because they also are considered drugs — the Food, Drug and Cosmetics Act. Under these laws, the FDA promulgates explicit rules, which can be found in Title 21 of the Code of Federal Regulations (CFR), that are binding on both the agency and industry.

Conforming to regulations enforced by the FDA's Center for Biologics Evaluation and Research (CBER), plasma collection operations must strictly follow their own standard operating procedures (SOPs) for donation and subsequent handling, freezing, storage and transportation of the plasma to the manufacturer for "fractionation" into immunoglobulins, coagulation agents, albumin and other therapeutic proteins. These SOPs help to ensure that products are free of contamination by transmissible agents. And, manufacturers incorporate CBER's "five overlapping layers of blood safety" in the collection of human plasma:

- plasma donor eligibility screening
- plasma testing for communicable diseases
- maintenance of donor deferral registries
- quarantine pending testing/records verification
- investigation and correction of system deficiencies

An important sixth "layer" of safety comes later during the fractionation process itself, when manufacturers employ multiple highly effective viral separation and inactivation methods.

Approving the Plant, and Policing the Process

Yet, even before any new plasma-based therapeutic is approved, CBER must inspect the production plant and review protocols for all process steps. CBER specifically seeks to determine whether the processes are well-validated and if there is sufficient quality assurance documentation in place. If everything complies with its "Current Good Manufacturing Practice" (cGMP) rules, CBER will grant an establishment license to the manufacturer, allowing it to make and distribute that product. Thereafter, CBER conducts plant inspections on a regular basis to assess whether products continue to be manufactured in compliance with applicable regulations.

And, with so many products made at so many facilities and spread across several continents, CBER recognized that the industry also needs to step up and police itself. So, a decade ago, in November 2000, the agency amended its regulations to require manufacturers to report any "biological product deviations" from cGMP standards or unforeseen events

that might affect product safety, purity or potency. Once such a "deviation" is reported, the manufacturer must demonstrate that it has corrected the problem.

This strategy of joint FDA-manufacturer accountability has clearly succeeded. And, it has succeeded in other ways as well. With joint technical workshops and formal comments on proposed regulations, for example, manufacturers and the FDA work in collaboration to ensure product safety and integrity.

One More Hurdle: Lot Release Testing

Once product is manufactured, CBER requires manufacturers to perform specific tests to ensure the purity, safety and content of active components for each lot (or batch) of a vaccine, plasma product or other biologic intended for human use. Samples from each lot accompany a release protocol that summarizes its production history and the results of all tests performed on it.

Some of the key lot release specifications for human immunoglobulin products, for example, include:

- physical appearance
- total protein content (g/dL)
- IgG antibody content (%)
- monomer and dimer content (%)
- product sterility (in vitro culture growth medium test)
- pyrogen (in vivo temperature elevation test)

CBER also may run confirmatory tests itself on some lots before allowing them to be released for distribution.

The Last Line of Defense: Post-Marketing Surveillance

Thanks to the layers of regulations, SOPs, inspections and testing, plasma products and vaccines that leave the plant almost invariably conform to their safety, potency and purity standards. But, we all know that a risk-free world remains an unattainable fantasy: There always will be that rare instance when a product somehow falls out of compliance without being detected. And, sadly, there always will be the few unscrupulous individuals who, for illegal gain, improperly tamper with products or attempt to redirect them through the hands of unauthorized or unlicensed parties.

To respond quickly to serious adverse events or therapeutic failures that might reflect an underlying product-related problem, the FDA relies on health professionals to voluntarily report them through its "MedWatch" Adverse Event Reporting System (AERS).

A separate surveillance program, the Vaccine Adverse Event Reporting System (VAERS), accepts reports from providers, manufacturers, patients, parents and guardians about adverse events thought to be associated with licensed vaccines. VAERS fields about 30,000 adverse event reports each year, some 10 percent to 15 percent of which involve permanent disability, hospitalization, life-threatening illness or death. And, most of the time — although not always — the association between the vaccine administration and one of these serious adverse events is entirely coincidental.

Thanks to the layers of regulations, SOPs, inspections and testing, plasma products and vaccines that leave the plant almost invariably conform to their safety, potency and purity standards.

However, if its review of these reports does lead the FDA to conclude that certain adverse events are directly related to the vaccine or other biologic, the agency can order that product to be recalled. And, just as important, reporting adverse events can lead to prompt corrective measures to address the product's manufacturing process, handling, storage and use. And, when suspicions that a product may be counterfeit provide to be valid, criminal investigations also will ensue.

Beyond FDA Regulation: The Industry's QSEAL Certification Program

To help define applicable FDA regulations and to extend beyond them, the Plasma Protein Therapeutics Association (PPTA) has developed its own standards and voluntary certification program for plasma sourcing and fractionation. Once an independent auditor inspects and reports on how closely a fractionator's policies, procedures and facilities adhere to its supplemental standards, PPTA makes the decision whether to award its QSEAL certification to that company. QSEAL is perhaps the most visible example of the industry's shared responsibility with the FDA to ensure product safety and integrity.

Of course, the beneficiaries of this industry self-scrutiny and unceasing FDA regulatory oversight are the patients who trust that every dose they receive contains exactly what they ordered. Nothing more and nothing less. ❖

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.*

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Gammaplex®, Immune Globulin Intravenous (Human), 5% Liquid, is indicated for the replacement therapy of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

CONTRAINDICATIONS
Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, is contraindicated in patients who have had an anaphylactic or severe systemic reaction to human immune globulin and in IgA-deficient patients with antibodies to IgA.

WARNINGS

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. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or those who are overweight or are receiving known nephrotoxic drugs. Gammaplex does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable.

See WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections in the Package Insert for important information intended to reduce the risk of acute renal failure.

Because this product is made from human plasma, it may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob [CJD] agent that can cause disease. The risk has been reduced by screening plasma donors for prior exposure, testing donated plasma and inactivating or removing viruses during manufacturing. Despite these measures, Gammaplex carries an extremely remote risk of transmission of viral diseases. The physician should discuss the risks and benefits of this product with the patient, before prescribing it to the patient.

All infections suspected by a physician possibly to have been transmitted by this product should be reported to FFF [800-843-7477] on behalf of Bio Products Laboratory.

Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, should only be administered intravenously.

PRECAUTIONS
General
The product should be used promptly after piercing the cap. Any partially used or unused product should be discarded. Visually inspect each bottle before use. Do not use if the solution is cloudy or turbid. Solution that has been frozen should not be used.

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

Renal dysfunction/failure
Ensure that patients with pre-existing renal deficiency are not volume depleted before infusion of IGIV. Periodic monitoring of renal function and urine output is particularly important in patients considered to be at increased risk of developing acute renal failure. Renal function, including blood urea nitrogen (BUN) and serum creatinine, should be assessed before administering Gammaplex and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Gammaplex.

Information for patients: Patients should be instructed to report the following signs and symptoms to their healthcare professional: decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage).

Hyperproteinemia, increased serum viscosity, and hyponatremia
Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV therapy. 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 Gammaplex at the minimum rate of infusion practicable.

Thrombotic events
Thrombotic events may occur following treatment with IGIV products. 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. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), hyperproteinemia or monoclonal gammopathies (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests). For patients judged to be at risk of developing thrombotic events, administer Gammaplex at the minimum rate of infusion possible.

Aseptic meningitis syndrome (AMS)
Aseptic meningitis syndrome (AMS) may occur infrequently with Immune Globulin Intravenous (IGIV) treatment, usually beginning within several hours to 2 days after IGIV. AMS may occur more frequently with high doses (2 g/kg) and/or rapid infusion of IGIV. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis
IGIV products can contain blood group antibodies (hemolysins) that coat red blood cells (RBCs) in vivo with immune globulin, resulting in a positive direct antiglobulin test (DAT). Acute hemolysis has been reported with IVIG. Delayed hemolytic anemia can develop due to RBC sequestration. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests).

Transfusion-related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema [Transfusion-related Acute Lung Injury (TRALI)] may occur in patients following IGIV treatment. Symptoms (fever, severe respiratory distress, pulmonary edema, hypoxemia but normal left ventricular function) typically appear within 1 to 6 hours following treatment. If TRALI is suspected, test for anti-neutrophil antibodies in both the product and the patient's serum (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests). Management of includes oxygen and appropriate ventilatory support.

Laboratory Tests
For appropriate monitoring, see previous sections on Renal, Hyperproteinemia, Hemolysis and TRALI.

Drug Interactions: Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella (see PATIENT COUNSELING INFORMATION).

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

ADVERSE REACTIONS
General
Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, contains no reducing carbohydrate stabilizers (e.g. sucrose, maltose) and no preservative.

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

Primary Humoral Immunodeficiencies (PI)
In a multicenter, open-label, non-randomized clinical study, 50 subjects with primary humoral immunodeficiency received 703 infusions with Gammaplex. Doses ranged from 279 to 799 mg/kg every 21 days (mean dose 465 mg/kg) or 28 days (mean dose 458 mg/kg), for up to 12 months. At some time during the study, all 50 subjects had an adverse event (AE) and in twenty-four subjects (48.0%) it was considered product-related.

The temporally associated AEs that occurred in more than 5% of subjects during a Gammaplex infusion or within 72 hours after the end of an infusion, *irrespective of causality* are given in the table below:

Adverse Event	Subjects (%) [n=50]	Infusions (%) [n=703]
Headache	18 (36%)	53 (7.5%)
Sinusitis	8 (16%)	9 (1.3%)
Pyrexia	7 (14%)	10 (1.4%)
Nausea	6 (12%)	7 (1.0%)
Pain	5 (10%)	5 (0.7%)
Chills	3 (6%)	5 (0.7%)
Fatigue	3 (6%)	9 (1.3%)
Hypertension	3 (6%)	4 (0.6%)
Insomnia	3 (6%)	3 (0.4%)
Nasal congestion	3 (6%)	3 (0.4%)
Upper respiratory tract infection	3 (6%)	5 (0.7%)
Vomiting	3 (6%)	3 (0.4%)

Five subjects (10%) experienced seven serious AEs. Two of these serious AEs were considered related to Gammaplex treatment (thrombosis and chest pain). Three other subjects withdrew from the study due to the following AEs: paresthesia, bronchospasm and pregnancy.

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).

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Bio Products Laboratory
a commitment for life

February 2010 GPX/09/30

Enhancing life's defenses

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

Positive efficacy outcomes
For PI patients receiving Gammaplex there were:
> No reports of Acute Serious Bacterial Infection
> Just 0.75 days per year of subjects hospitalized[1]
> Only 2.36% of subjects out of work/school/day care[1]

Low IgA levels
> The content of IgA is <10 µg/mL[1]

Convenient infusion schedule
> Infusion rate can be increased every 15 minutes to a maximum rate of 0.08 mL/kg/min[1]

Robust 3-step virus reduction
> An extremely low risk of viral transmission

Room temperature storage
> Gammaplex can be stored between 2°C and 25°C (36°F to 77°F) unopened for 2 years

IMPORTANT SAFETY INFORMATION
Gammaplex is indicated for the replacement therapy of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

WARNING: Renal dysfunction, acute renal failure, osmotic nephropathy and death may be associated with the administration of 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. Gammaplex does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable. See full prescribing information for complete boxed warning.

Gammaplex is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to human immune globulin and in patients with selective IgA deficiency and in patients with a history of hypersensitivity.

In patients at risk of developing renal failure, monitor urine output and renal function including blood urea nitrogen (BUN) and serum creatinine. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. Thrombotic events may occur following treatment with Gammaplex and other IGIV products. Monitor patients with risk factors for thrombotic events, including a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known/suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) may occur infrequently with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. Hemolysis and hemolytic anemia can develop subsequent to IGIV treatments. Noncardiogenic pulmonary edema may occur in patients following IGIV treatment (i.e. transfusion-related acute lung injury [TRALI]). Monitor patients for pulmonary adverse reactions (TRALI). Test product and patient's serum for anti-neutrophil antibodies.

Gammaplex 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 Gammaplex were headache, fatigue, nausea, pyrexia, hypertension, myalgia, pain and vomiting.

REFERENCES
1. BPL. US Prescribing Information, data on file. VSUS1PI, September 2009.

Please see the adjacent Brief Summary of Prescribing Information including boxed warning.

Bio Products Laboratory
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1-800-843-7477

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It Couldn't Happen to Me

For many, the 2009 H1N1 pandemic is nothing more than headline news. But when you go from reading about statistics to becoming one, vaccine compliance hits much closer to home.

BY TRUDIE MITSCHANG

AS I LAY bedridden in the emergency room (ER) just days after Thanksgiving, an IV in my arm and an oxygen mask on my face, I had to concede the H1N1 virus was a force to be reckoned with. The pandemic-grade flu bug had literally knocked me flat on my back, so I had plenty of time to think about the decisions and circumstances that had landed me there.

It started as a tickle in my throat. As I sat down at my desk that November morning, I felt tired. Thanksgiving was just 48 hours away, and my to-do list was only half completed. By 10 a.m., I was starting to cough a bit, and on my way to the printer I suddenly felt weak. As body aches and fatigue set in, so did a low-grade panic. "Tell me I'm not getting the flu!" I thought. But it was too late for positive thinking. By the time I left work an hour later, I already had a fever. H1N1 had struck again. Looking back, I see now that things could have been different.

My decision to forgo vaccination was rooted in common excuses: "I never get sick." "I'm not sure flu shots work." And, "How bad could it be? I'll take my chances."

Despite many opportunities to get the 2009 H1N1 vaccine, I had intentionally opted out. My decision to forgo vaccination was rooted in common excuses: "I never get sick." "I'm not sure flu shots work." And, "How bad could it be? I'll take my chances." This is where the story gets embarrassing. The Centers for Disease Control and Prevention (CDC) reports that as of January 2010, only 20 percent of the U.S. population was vaccinated against the H1N1 flu virus, but the fact that I was in the 80 percent majority provided little comfort. The thing is, I'm a staff writer for FFF Enterprises, "the nation's largest and most trusted distributor of flu vaccine" and the publisher of this magazine. Which means, I'd spent the better part of 2009 writing articles, press releases and marketing

materials that explained how important it is to get the 2009 H1N1 flu shot. And, I didn't just write — I researched. I knew the statistics. I even knew that as an adult with asthma, I am in a high-risk group especially vulnerable to serious flu complications. I still thought the odds were in my favor, so I decided to roll the dice.

Initially my flu symptoms were somewhat mild: low fever, lots of body aches, chills and fatigue. Lousy, but no big deal until about day five, when I began wheezing and was unable to catch my breath, quite suddenly in desperate need of medical assistance. Although my condition was stabilized after four hours in the ER and did not require an overnight hospital stay, not everyone in my family was as fortunate.

All in the Family

One month almost to the day that I contracted H1N1, my husband, Jeff (who also avoided a flu shot), began coughing. It was Dec. 22, and our planned flurry of holiday parties and outings came to a screeching halt. Antibiotics, bed rest and chicken soup helped ease the symptoms, but 10 days into his ordeal, Jeff was admitted to the hospital with pneumonia. He is not in a high-risk group and has no outstanding health problems. Since he was fit, active and highly health-conscious, you'd expect him to bounce back fairly quickly; it was three weeks before he fully recovered and started to feel "normal" again.

When I was sick, my lowest moment was not in the ER. It was sitting at the Thanksgiving dinner table and realizing I had exposed my young children and my 80-year-old parents to a disease that I would likely fight off, but which could prove deadly for any of them.

Do As I Say, Not As I Do

Is there a moral to this story? My obvious point is to encourage others not to make the same mistakes we did. But I've read these kinds of personal accounts too, and I know it's not easy to motivate change with a magazine article. Still, I would ask those who have resisted getting flu shots out of habit, ignorance or belief systems that no longer serve them to please reconsider. When I was sick, my lowest moment was not in the ER. It was sitting at the Thanksgiving dinner table and realizing I had exposed my young children and my 80-year-old parents to a disease that I would likely fight off, but which could prove deadly for any of them. My husband works with young children and families; who knows how many people he exposed to the virus? I suddenly saw our decision to avoid vaccination as not merely personal but purely selfish. It's a perspective worth considering.

They say experience can be a harsh teacher. This is one reluctant student who has learned her lesson well. ❖

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

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.

Manufactured by:

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U.S. License No. 1646

Distributed by:

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Hoboken, NJ 07030

octapharma

For the safe and optimal use of human proteins

From the Octapharma Family to your Family

Von Willebrand Factor / Coagulation Factor VIII Complex (Human)

Our Family
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.

Our Commitment
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
usmedicalaffairs@octapharma.com

Customer Service / 866-766-4860
uscustomerservice@octapharma.com

Reimbursement / 201-604-1123
usreimbursement@octapharma.com

Inventing Tomorrow Today

"The ultimate test for a leader is not whether he or she makes smart decisions and takes decisive action, but whether he or she teaches others to make smart decisions and take decisive action."

— Noel M. Tichy

BY TRUDIE MITSCHANG

STRAIGHTFORWARD IS DEFINITELY a word you would use to describe Flemming Nielsen. The Denmark native says he was raised to challenge rules and think outside of the box — Scandinavian traits that have served him well as the president of Octapharma USA, Inc. Under his leadership, the company maintains a highly entrepreneurial spirit, encourages innovation and values people who are willing to execute on ideas, even at the risk of failure.

We truly believe that the biggest resource we have here is human capital, and we invest heavily in each individual's personal and professional growth.

"We encourage our team members to not only succeed, but to also be willing to accept failure — just don't fail at the same thing twice!" Nielsen says. "At Octapharma, we try to step outside of the traditional business model. Naturally, we have a plan and strategy in place, but we also understand the need to divert from that plan at times; if the plan is wrong, you have to be prepared to change directions. At the end of the day, success will not be measured solely on your plan, but on your execution."

A Leader in the Plasma Market

Since its founding in 1983, Octapharma has become one of the key players in the global plasma market for plasma derivatives and is active in more than 70 countries around the world. With more than 3,000 employees, the company is continuously expanding. Nielsen joined Octapharma in 2003 at the company's headquarters in Switzerland, but soon transferred to the U.S. where he has been instrumental in Octapharma's successful track record in the U.S. market: In just a little more than four years since the launch of its first product, Octapharma USA, Inc., has captured approximately 10 percent of the marketplace for intravenous immune globulin (IVIG).

"Our biggest accomplishment in the U.S. market is that we have managed to position Octapharma as a reliable and trustworthy business partner that truly walks the talk," Nielsen says. "The growth of Octapharma USA and the expansion and success of the U.S. commercial operations over such a short time frame is an accomplishment in which we all take great pride."

Leading by Example

When it comes to leadership style, Nielsen endeavors to lead by example, empowering team members to take ownership of initiatives and ideas, encouraging collaboration and providing team-building activities that remove the restrictions imposed by boardroom dynamics. A recent company outing took the sales team to Denmark and Sweden for a week of outdoor adventure aimed at challenging the body, the mind and the spirit.

"You establish different interactions with one another when you interact as human beings, not just as co-workers," he explains. "We truly believe that the biggest resource we have here is human capital, and we invest heavily in each individual's personal and professional growth."

Making Safety the Priority

Since its inception, Octapharma has placed the highest priority on safety; an often-quoted saying among company executives is: "If it's safe for patients, it's safe for the company." The company mission statement, "For the safe and optimal use of human proteins," further exemplifies its passion for providing life-saving and life-enhancing therapies for the patients who need them. This mission statement has stood the test of time, driving Octapharma's activities for more than two decades. In addition to its plasma-based activities, Octapharma has recently dedicated increasing resources to recombinant product research and development based on the use of human cell lines.

"From the early stages of product development and licensure trials, to the commitment for post-marketing research, Octapharma builds trust not only in the developmental stages of its products, but also in their real-world utilization," explains Nielsen. "This is seen across the world in our efforts and commitment to post-marketing surveillance for products, such as our immune globulins, Octagam 5% and Octagam 10%, as well as for our von Willebrand factor product, Wilate."

Innovative Entrepreneurs

One of Octapharma's core values is innovation, and Nielsen notes that there are extensive product development activities underway in each of its three major therapeutic focus areas: immunotherapy, hematology and intensive care/emergency medicine. The company also is proceeding with worldwide efforts to expand its immune globulin portfolio with both enhanced formulations, including subcutaneous therapy and expanded indications.

"Our hematology portfolio is of unique interest, as we have not only recently received both FDA approval and orphan drug exclusivity status for Wilate, but we are now beginning our U.S. clinical development efforts for our human cell line recombinant factor VIII product, which is most exciting," adds Nielsen.

Many people have a motto or creed that drives their approach to business and life. For Nielsen, leading a company known for trailblazing requires a willingness to pull out the proverbial crystal ball. He calls this trait the ability to "invent tomorrow today."

"A lot of people confuse leadership with management," Nielsen explains. "Management is controlling, whereas leadership is inspiring. If I'm doing my job the right way, I am constantly looking forward to anticipate what's ahead. As a company, we are constantly evolving. We're a different organization than we were in 2004, or 2006, and we will be different a year from now than we are today. Of course, as we branch into new areas, we will always maintain our core values as 'innovative entrepreneurs.' It's what our company was founded on." ❖

You establish different interactions with one another when you interact as human beings, not just as co-workers.

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

BioProducts

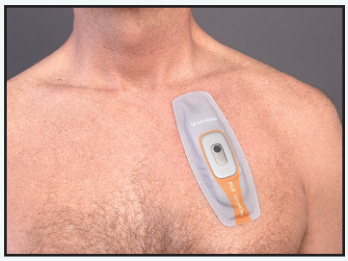
Medical Record Retrieval System

MediConnect, recently selected by the Obama administration to provide electronic personal health records for Medicare beneficiaries, is a medical record retrieval system designed to make ordering records simple and fast. Insurance companies, legal firms, health professionals and individuals can all use MediConnect's secure online process to order, receive and track records, and MediConnect Global negotiates and pays all medical provider fees directly. The system can integrate to most major case and agency management software solutions and any custom enterprise system, allowing records to be ordered and received directly within the office management system of choice. All services are accessible 24/7 from anywhere in the world via a standard web browser. There is no software to buy or download. Payers sign up for a free account and pay only for the services used.
MediConnect Global, (800) 489-8710, www.mediconnect.net

Medication Dispensing System

The Omnicell Mobile Medication System, a fully integrated, closed-loop and transportable solution, is designed for safe and secure transportation of medications from the automated dispensing cabinet to the patient bedside. The system provides clinicians with a fully integrated solution that includes Omnicell's SafetyMed and the new Anywhere RN software to reduce the risk of medication errors and increase workflow efficiencies. Anywhere RN enables remote access to many automated dispensing cabinet functions, while SafetyMed verifies the "five rights" of medication administration at the point of care. For clinical staff, the system offers guiding lights technology and advanced two-dimensional bar code capabilities for patient identification and medication administration verification. The closed-loop solution also enables real-time reconciliation by identifying which medications have been administered compared to what has been issued from the automated dispensing cabinet.
Omnicell Inc., (800) 850-6664, www.omnicell.com

Mobile Cardiovascular Monitor



The Nuvant Mobile Cardiac Telemetry (MCT) System is a wireless cardiovascular solution to diagnose symptomatic and asymptomatic cardiac arrhythmias and proactively manage patients remotely from anywhere across the globe. The system leverages the low-profile form factor, advanced algorithms and multi-sensor capabilities of the PiiX wearable platform to enable continuous monitoring for a broad set of arrhythmias, including atrial fibrillation, as well as patient falls that may be associated with arrhythmias. Patients also can trigger the collection of an electrocardiogram (ECG), on demand, upon experiencing symptoms. All ECGs are transmitted to the Corventis Monitoring Center via the wireless-enabled zLink for review and response by trained cardiographic technicians. Physicians receive notification of urgent events, as well as actionable information in the form of Episode Reports, Daily Reports and End of Use Reports via fax, email and/or the secure website.
Corventis, (408) 790-9393, www.corventis.com

PIDD Recognition and Tracking

The SPIRIT (Software for Primary Immunodeficiency Recognition Intervention and Tracking) Analyzer is designed to be used by managed care plans as a diagnostic tool to identify undiagnosed patients with PIDDs. It includes a list of more than 350 weighted ICD 9 codes that are matched to the 10 warning signs of PIDD to establish low-, moderate- and high-risk categories. Patients who score moderate and high risk are flagged as potentially in need of further testing for PIDD. SPIRIT can analyze one million pharmacy and medical claims in approximately 30 minutes. Health plans are able to automatically alert the physicians of those patients with recurring infections who are high and moderate risk to encourage appropriate assessment to improve patient outcomes and save healthcare costs. The analyzer is currently being pilot tested by third-party payers.
Jeffrey Modell Foundation, (866) 463-6474, www.info4pi.org

When thrombotic risk is high in hereditary antithrombin deficiency

Proceed Safely

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

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

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

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

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

Important Safety Information

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

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

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

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

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

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

Talecris BIOTHERAPEUTICS

Thrombate III® antithrombin III (human)

Printed in USA November 2009 TH86-1109

THROMBATE III®
Antithrombin III (Human)

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

FOR INTRAVENOUS USE ONLY

DESCRIPTION

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

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

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

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

INDICATIONS AND USAGE

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

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

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

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

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

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

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

PRECAUTIONS

General

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

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

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

Laboratory Tests

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

Drug Interactions

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

Pregnancy Category B

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

Pediatric Use

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

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

ADVERSE REACTIONS

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

CAUTION

℞ only

U.S. federal law prohibits dispensing without prescription.

Talecris BIOTHERAPEUTICS

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BioResearch

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

Therapeutic Plasma Exchange Permits ABO-Incompatible Kidney Transplantation

Because of the shortage of cadaveric donor kidneys and varying frequencies of each major blood group, more than 4,000 U.S. patients die annually waiting for a kidney transplant. In a review of 46 cases, a team at Johns Hopkins Hospital has documented that therapeutic plasma exchange (TPE) with 5% albumin replacement reduced ABO titers sufficiently to permit transplants of ABO-incompatible (ABO-I) kidneys.

All patients received a mean of 6.2 pre-transplantation and 5.0 post-transplantation TPE procedures, with low-dose infusion of CMVIg (CytoGam, CSL Behring) following each procedure. CMVIg is a potent immunomodulator that is thought to suppress de novo antibody production. There was excellent allograft performance in all patients and no episodes of hyperacute rejection or graft loss from antibody-mediated rejection. TPE reduced mean AHG phase ABO titers from 64 to 8 prior to transplantation; titers remained very low three to six months after transplantation. One-year graft survival was 100 percent. TPE treatments resulted in minimal complications. A combination of TPE and CMVIg is now a mainstay of the institution's ABO-I renal transplantation program.

Tobian, AAR, Shirey, RS, Montgomery, RA, et al. Therapeutic plasma exchange reduces ABO titers to permit ABO-incompatible renal transplantation. Transfusion*, 2009 Jun;49(6):1248-54.*

IVIG Cuts Mortality in Infants with Acute Myocarditis

In contrast to six deaths in 13 infants (46 percent) treated with conventional supportive care for severe acute myocarditis, just one of 12 infants (8 percent) who additionally received high-dose (2 gram/kg) IVIG died during their hospitalization, according to a review of all cases between 2004 and 2007 admitted to the Aga Khan University Hospital in Karachi, Pakistan. This striking mortality difference was statistically significant ($p = 0.04$). Pakistani hospitals generally do not have access to mechanical circulatory support technology (which contributes to higher mortality in cases of severe myocarditis) commonly used in the U.S.

All patients had antecedent gastrointestinal or respiratory illness, hepatomegaly, pulmonary edema and metabolic acidosis. Baseline ejection fraction in the two groups was not significantly different (17.5 percent and 22.5 percent). Children with pre-existing structural heart defects, cardiomyopathy, coronary anomalies, sepsis or Kawasaki disease were excluded.

While acknowledging limitations that included a small sample size and a retrospective study design, the authors concluded that their findings "provide support for aggressive supportive care and early use of IVIG in acute myocarditis in children."

Haque, A, Bhatti, S, and Siddiqui, FJ. Intravenous immune globulin for severe acute myocarditis in children. Indian Pediatrics*, 2009 Sep;46(9):810-11.*

Subcutaneous Ig as Alternative to IVIG in Multifocal Motor Neuropathy

Weekly or twice-weekly infusions of subcutaneous immunoglobulin (SCIG) at home were able to maintain muscle strength in four of five patients with multifocal motor neuropathy (MMN) who were crossed over from IVIG maintenance therapy, according to Dutch investigators. However, this result occurred only when patients received a total dose of IgG antibody equivalent to their prior IVIG maintenance dose. In another group of four subjects given SCIG at 50 percent of their prior IVIG maintenance dose, all four experienced deterioration in grip strength, pinch strength and dexterity.

Local adverse events — most commonly swelling and redness at the injection site — were reported by all patients during their six-month monitoring period; the frequency of these non-serious events declined over time. Throughout 330 total treatments, just nine mild systemic adverse events (fever, malaise, palpitations and skin rash) were reported by three patients, all but two of which occurred in the first week of therapy. There were no reported serious adverse events. The authors concluded that SCIG and IVIG were equally effective in achieving stable muscle strength in four of five subjects given an equivalent dosage of IgG immunoglobulin, and treatment was generally well-tolerated with only mild local and systemic adverse events.

Eftimov, F, Vermeulen, M, de Haan, RJ, et al. Subcutaneous immune globulin for multifocal motor neuropathy. Journal of the Peripheral Nervous System*, 2009 Jun;14(2):93-100.*

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.*

BioDashboard

CALCULATOR

IVIG Reimbursement Calculator

Product	Manufacturer	HCPCS	Reimbursement Rates: Hospital Outpatient ASP+4% (per gram)	Reimbursement Rates: Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$60.559	$61.724
FLEBOGAMMA 5% DIF	Grifols	J1572	$72.623	$74.02
GAMMAGARD LIQUID	Baxter BioScience	J1569	$75.60	$77.054
GAMMAGARD S/D	Baxter BioScience	J1566	$60.559	$61.724
GAMUNEX	Talecris Biotherapeutics	J1561	$73.83	$75.25
OCTAGAM	Octapharma	J1568	$73.954	$75.376
PRIVIGEN	CSL Behring	J1459	$68.877	$70.202

Calculate your reimbursement online at www.fffenterprises.com/Resources/IVIGCalculator.aspx

Rates are effective April 1, 2010 through June 30, 2010.

REFERENCE TABLES

IG Reference Table

Product	Size	Manufacturer	Indications
CARIMUNE NF (Lyophilized)	3 g, 6 g, 12 g	CSL Behring	PIDD, ITP
FLEBOGAMMA 5% DIF (Liquid)	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols	PIDD
GAMMAGARD LIQUID (10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Baxter BioScience	PIDD
GAMMAGARD S/D (Lyophilized, 5% or 10%)	2.5 g, 5 g, 10 g	Baxter BioScience	PIDD, ITP, CLL, KD
GAMUNEX (Liquid, 10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Talecris Biotherapeutics	PIDD, ITP, CIDP
GAMMAPLEX (Liquid, 5%)	2.5 g, 5 g, 10 g	Bio Products Laboratory	PIDD
HIZENTRA (Liquid, 20%, SCIG)	5 mL, 10 mL, 20 mL	CSL Behring	PIDD
OCTAGAM (Liquid, 5%)	1 g, 2.5 g, 5 g, 10 g, 25 g	Octopharma	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
AFLURIA Pediatric	0.25 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90655
FLUZONE Pediatric	0.25 mL prefilled syringe		
AFLURIA	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
FLUZONE	0.5 mL single-dose vial		
FLUVIRIN	0.5 mL prefilled syringe		
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
FLUZONE	5 mL multi-dose vial		
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to individuals 3 years and older, for intramuscular use	90658
FLUVIRIN	5 mL multi-dose vial		
FLUZONE	5 mL multi-dose vial		
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

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For the treatment of hemophilia A

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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.

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