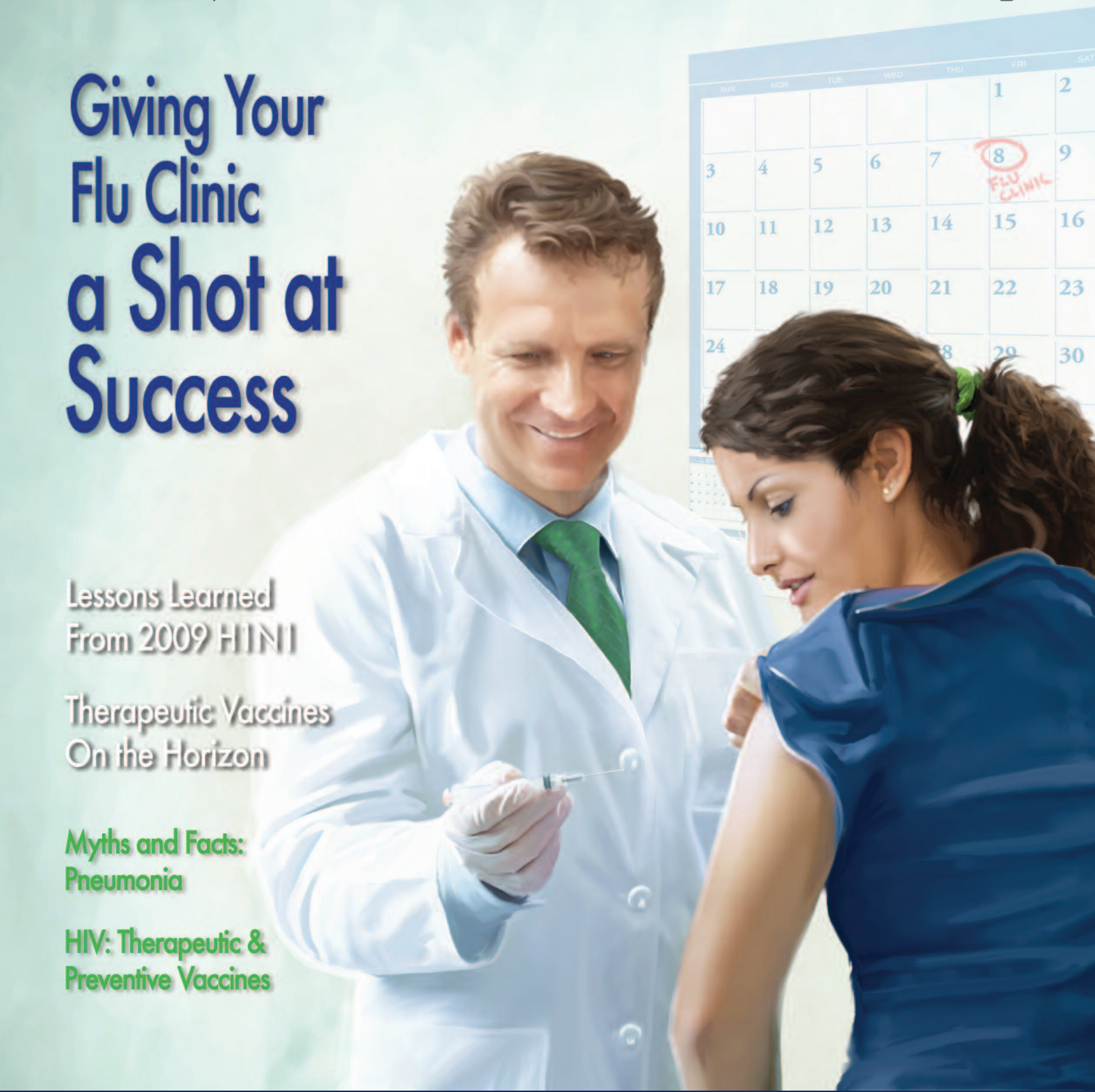
July 2010

BioSupply Trends

Special Focus: VACCINES

Quarterly

Giving Your Flu Clinic a Shot at Success



Lessons Learned From 2009 H1N1

Therapeutic Vaccines On the Horizon

Myths and Facts: Pneumonia

HIV: Therapeutic & Preventive Vaccines

The Research Behind Early Cancer Detection — Page 38

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

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

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Warnings and Precautions - Hyperproteinemia 8/2008

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

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

INDICATIONS AND USAGE

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

HOW SUPPLIED

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

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www.octapharma.com/usa

A clear solution

IMPORTANT SAFETY INFORMATION

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

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

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

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

See brief summary of PI on facing page.

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

octagam®

Immune globulin intravenous (human)
5% liquid preparation

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

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

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

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

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

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

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

octapharma

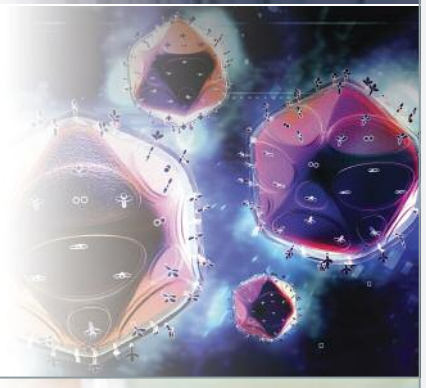
For the safe and optimal use of human proteins

BioSupply Trends Quarterly

July 2010

Features

Special Focus: Vaccines



Up Front

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

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An Ounce of Prevention

THERE IS a saying in the industry: When you've seen one flu vaccine season, you've seen one flu vaccine season. Unpredictable at best, influenza (flu) and its vaccine are forces to be reckoned with. Consider that according to the Centers for Disease Control and Prevention (CDC), more people die each year from influenza and resulting complications than from all vaccine-preventable diseases combined. Another little-known fact is that influenza and pneumonia combined are the eighth leading cause of death in the U.S. The influenza vaccine also is the only vaccine that requires a new inoculation each year because the vaccine is reformulated annually to protect against the three virus strains that are expected to be most prevalent. Yet, despite these facts, more myths surround the flu and its vaccine than almost any other common disease today.

As I write this letter, I cannot help but reflect upon where we were last year at this time. We were launching our inaugural publication of *BioSupply Trends Quarterly* just as news of a new pandemic influenza strain dominated the media and shifted the focus of manufacturers, government agencies and healthcare providers overnight. We were unaware when we chose vaccines as our first issue's theme how topical it would be, and now one year later, we take a look at lessons learned from H1N1.

One of the positive impacts of last year's pandemic was certainly the media attention that raised public awareness and understanding of this deadly disease. That our actual flu season was much milder than usual may allow apathy to creep back in, but our hope is that we can leverage this increased awareness to boost vaccination rates. Those on the front lines are best suited to keep this awareness high and help turn the tide on vaccine resistance.

With the debate over healthcare reform also dominating the media, and the recent measure being passed into law, prevention also is a topic high on everyone's agenda. Not unlike many of today's innovations that we take for granted, such as the Internet, antibiotics and the iPhone, vaccines are perhaps one of the greatest man-made discoveries of the 20th century. Imagine living in the days when polio or measles were common diseases with no known cure. Yet there is still an anti-vaccine movement to be reckoned with. I was pleased to see that our April feature, Counteracting the Anti-Vaccine Movement: Promoting an Ounce of Prevention, received many requests for reprints from healthcare professionals who valued it as a communication tool for their patients. With nine new measles outbreaks being reported so far in 2010 (as many as during all of 2009), it is imperative that we deal with any apathy or misinformation regarding the safety and efficacy of vaccines that have all but eradicated once-deadly diseases.

In this issue, we look at therapeutic vaccines. While not all diseases are vaccine-preventable, these new vaccines to treat pre-existing conditions, such as HIV, cancer, multiple sclerosis, shingles, Alzheimer's and others, have the potential to radically change medical treatment. This may seem futuristic, but there are actually three vaccines that have already gained regulatory approval in the U.S.: one for multiple sclerosis, one for shingles and, most recently, one for prostate cancer. Others are showing very promising results at various stages of clinical trials.

As Vas Narasimhan of Novartis Vaccines states so eloquently in his leadership profile, "Vaccines are the most transformative public health development of the past hundred years." We are fortunate to be on this critical, innovative path to prevention. As always, we hope you find this issue educational and valuable to you and your colleagues. ❖

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

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

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Healthcare Reform 2010: Federal Update

Many questions remain unanswered about the healthcare reform recently enacted into law. While the law will not provide healthcare for every U.S. citizen, the number of citizens eligible for healthcare will increase by approximately 32 million. However, how the law will affect citizens requiring special healthcare needs is uncertain. For instance, it is still unclear whether it will improve access to care for those who have chronic illnesses, rare diseases and genetic disorders — who also rely on plasma-derived therapies and their analogues, vaccines and other biologics. All we can be sure of now is the bill's key provisions.

Private Insurance Reform

• Bans discrimination against children with pre-existing conditions within six months of the law's passage (effective for adults no later than 2014).

• Bans recisions effective within six months (health plans are banned from dropping people from coverage if they get sick).

• Bans lifetime caps on coverage within six months.

• Regulates annual limits on coverage within six months, and restricts new plans' use of annual limits to ensure access to needed care (beginning in 2014, the use of any annual limits would be prohibited for all plans).

• Requires free preventive care under new plans (no copays and deductibles) effective within six months.

• Creates a new independent internal and external appeals process for new plans effective within six months.

Uninsured Reform

• Establishes an interim high-risk pool for the uninsured with pre-existing conditions (effective 90 days until state exchanges are up and running by 2014).

• Extends coverage for young adults up to their 26th birthday through their parents' insurance policy (effective within six months).

Medicare Reform

• Begins to close the Medicare Part D doughnut hole by providing a $250 rebate to Medicare beneficiaries who hit the doughnut hole in 2010 (beginning in 2011, the law institutes a 50 percent discount on brand-name drugs in the doughnut hole, and by 2020, it completely closes the doughnut hole).

• Eliminates copayments for preventive services, and exempts preventive services from deductibles under the Medicare program (effective Jan. 1, 2011).

• Creates a temporary reinsurance program (until the state exchanges are available) to help offset the costs of expensive health claims for employers that provide health benefits for retirees age 55 to 64 (effective 90 days after enactment).

Other Reform

• Increases funding for community health centers to allow for nearly doubling the number of patients served during the next five years (effective 2010).

• Provides new investment in training programs to increase the number of primary care doctors, nurses and public health professionals (effective 2010).

• Provides aid to states to establish offices of health insurance consumer assistance to help file complaints and appeals (effective 2010).

• Creates a long-term insurance program financed by voluntary payroll deductions to provide benefits to adults who become functionally disabled (effective Jan. 1, 2011).

• Establishes a regulatory pathway for FDA approval of biosimilar versions of previously licensed biological products. ❖

Healthcare Reform 2010: State Update

While Congress was busy debating healthcare reform, the states were busy introducing bills sponsored by patient organizations to ensure that those with chronic illnesses and rare diseases have continuity of care and access to medications prescribed by their physicians (rather than their insurance companies), as well as to ban the practice of specialty tiers and cap the out-of pocket costs for prescriptions. The number of states introducing legislation this year has increased. They include California, Florida, Hawaii, Maryland, Minnesota, Missouri, Nebraska, New York and Ohio, among others. It is expected that the attention the bills receive in these states this year will result in reforms in 2011.

While the National Multiple Sclerosis Society has been one of the most active and organized of the patient organizations calling for legislation, other organizations also have taken part, including the Hemophilia Federation of America and the Alliance for Plasma Therapies, whose membership includes the American Partnership for Eosinophilic Disorders, the A-T Children's Project, the Foundation for Peripheral Neuropathies, the International Pemphigus & Pemphigoid Foundation, The Myositis Association, the Neuropathy Action Foundation, The Neuropathy Association and the Platelet Disorder Support Association. These organizations are working together to analyze all bills and to utilize the grass-roots strength of chapters and support groups to make next year the "The Year of the Patient."

Currently, the state bills include:

• *California — AB 2170: Prescription Drug Coverage under Formularies.* Prohibits a healthcare service plan or a health insurer that covers prescription drug benefits and uses a formulary from changing the applicable copayments, deductibles or coinsurances for prescription drug benefits for the length of the contract or policy.

• *Florida — HB 275 and SB 516: Prescription Drugs Insurance Coverage.* Prevents health insurance plans from prohibiting, limiting, switching, reducing or denying prescription drug coverage during the plan year, and provides for continuity of care for Florida's consumers.

• *Hawaii — HB 2461: Continuity of Care Legislation.* Requires health insurers and like entities to offer at least the same drug coverage to the insured that they had under their previous policy with a different insurer or like entity.

• *Maryland — HB 478 and SB 663: Cost-Sharing Obligations Legislation.* Prohibits specified insurers, nonprofit health service plans and health maintenance organizations from imposing a cost-sharing obligation for a prescription drug that exceeds the dollar amount of the cost-sharing obligation; also prohibits allowing unfair discrimination between individuals for the amount of the cost-sharing obligation for a prescription drug.

• *Minnesota — SF 2816: Limitation on Enrollee Cost-Sharing for Biologic Prescription Drugs.* Ensures that enrollees who are prescribed FDA-approved biologic products are charged a copayment, coinsurance or deductible that does not exceed their health plans' lowest-cost, nonpreferred, brand-name FDA-approved medication in the prescription plan formulary.

• *Nebraska — LB 1017: Ban on Specialty Tiers and Coinsurance for Prescription Medications.* Eliminates specialty tiers and coinsurance, and caps out-of-pocket expenses for prescription medications at $1,000 for an individual policy and $2,000 for a group policy.

• *Nebraska — LB 1088: Physician and Patient Prescription Protection Act.* Requires written communication to the physician and patient when the patient's medication prescribed by that physician is to be changed (written communication must include any information about risks associated with the recommended medication change and an explanation of any financial incentives driving the switch in medication).

• *New York — A 6298 and S 191: Bans on Specialty Tiers and Cost-Sharing for Prescription Medication.* Instructs the superintendent of insurance to deny policies that impose drug tiers based on expense or disease category and that charge a cost-sharing percentage for prescription medication.

• *Ohio — HB 453: Continuity of Care Legislation.* Prohibits healthcare insurers from removing a prescription drug from its formulary, moving a covered prescription drug to a higher copay tier, and making certain changes with respect to prescription drug coverage without providing written notice to the healthcare providers, pharmacies, pharmacists and persons with healthcare coverage who will be affected by the changes. ❖

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.

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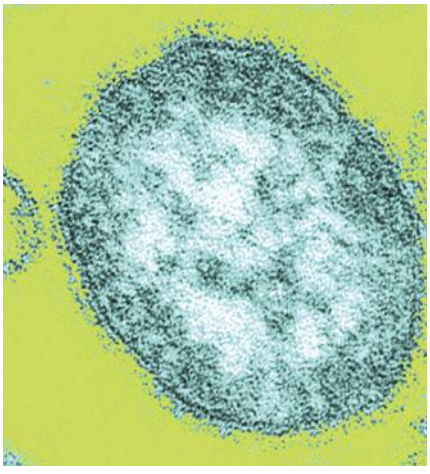
Safety

Warning of New Measles Outbreak

The California Department of Public Health (CDPH) released a health advisory in April concerning a potential measles outbreak. As of this writing, nine cases of measles have been reported in California in 2010, which is as many cases in all of 2009. As in recent years, nearly all of the cases are known to have traveled recently to Europe or Asia or have been in contact with international travelers, and some of the cases have been intentionally unvaccinated children.

The CDPH states that the recent cases in California highlight the need for healthcare professionals to be vigilant about measles. To stop the spread of the disease, physicians are asked to consider measles in patients of any age who



have a fever and a rash. Fever can spike as high as 105 degrees Fahrenheit. Measles rashes are red, blotchy and maculopapular and typically start on the hairline and face and then spread downward to the rest of the body. In addition, physicians are advised to obtain a thorough health history of such patients, including travel outside of North America or contact with international travelers in the prior three weeks, as well as prior vaccinations for measles. If measles is suspected, the individual should be isolated and the local health department should be alerted. Once diagnosed, specimens of measles should be collected for testing.

For more information about what to do if measles is suspected, visit www.cdph.ca.gov/programs/immunize/Documents/CDPH_MeaslesHealthAdvisory_April2010.pdf. ❖

Healthcare

New Tax Incentive for Biotech Companies

The recently enacted healthcare legislation contains a new incentive for biotech companies known as the Qualifying Therapeutic Discovery Project Credit (Therapeutic Credit). Enacted as Sec. 48D of the Internal Revenue Code, the Therapeutic Credit will allow some businesses to claim a credit for 50 percent of their qualified investment in qualifying therapeutic discovery projects for 2009 and 2010. Two aspects set this incentive apart from similar programs. First, it is available only to businesses with 250 or fewer employees. Second, taxpayers may elect to receive grants in lieu of tax credits.

Qualifying therapeutic discovery projects include those designed to accomplish the following: treat or prevent diseases or conditions by conducting pre-clinical or clinical activities for the purpose of securing Food and Drug Administration approval of a product; diagnose diseases or conditions, or determine the molecular factors related to diseases or conditions, by developing molecular diagnostics to guide therapeutic decisions; or develop products, processes and technologies to further the delivery or administration of therapeutics.

However, the Therapeutic Credit is not available to all eligible businesses that apply. Because there is a limited pool of money allocated to these credits/grants, the Treasury will review and select applicants based on the project's potential to result in new therapies for areas of unmet need or to prevent, detect or treat chronic or acute diseases or conditions; reduce long-term healthcare costs or advance the goal of curing cancer within 30 years; and advance U.S. competitiveness in biotechnology while creating and sustaining high-paying jobs in the U.S.

For more information about the Therapeutic Credit, go to www.forbes.com/2010/03/26/health-reform biotech-tax-credit-personal-finance dean-zerbe.html. ❖

Did You Know?

It's possible to prevent rabies if immunization is given within two days of a bite. To date, no one in the United States has developed rabies when given the vaccine promptly and appropriately.

Research

Cialis to Fight Cancer?

Doctors at The Johns Hopkins Hospital are testing to see if Cialis, the erectile dysfunction drug, can help people with cancer. A new clinical trial is studying whether the drug's tumor-fighting benefits have the potential to help those fighting head and neck cancer. The link between erectile dysfunction drugs and cancer treatment was first discovered by a Johns Hopkins oncology researcher who conducted studies in mice and human blood samples, all of which showed improvement in the immune response of patients who received Cialis. Other research conducted using Viagra also was successful. However, researchers believe it has too short of a half-life to offer the same benefits as Cialis, which has a half-life that is twice as long.

Researchers are enrolling patients in the clinical trial, which is funded by a grant from the National Cancer Institute. Patients are given a once-daily dose of Cialis for 10 to 14 days. At the end of the test period, their blood samples are looked at to determine the drug's success in boosting the immune system. Patients then proceed with their recommended treatment protocol, whether it's surgery, chemotherapy or radiation. Right now, doctors consider Cialis primarily as a complement to other standard therapy. In the future, there is potential that the drug could lessen or eliminate the need for chemotherapy or radiation. ❖

Safety

New Vaccine System Helps Protect Pregnant Women

The American Academy of Allergy, Asthma and Immunology has launched a new system to provide information to pregnant women and their doctors about using medications and vaccines safely during pregnancy. The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) collects information from women who are pregnant or have recently completed their pregnancies in order to provide information on issues that could be of concern to women and their babies.

VAMPSS obtains comprehensive information on various medicine and vaccine exposures, including those exposures that are unlikely to be included in the woman's medical record. Mothers are asked about all medicines taken, regardless of whether they were prescribed, purchased over the counter, on the Internet or borrowed from others. They also are asked about all vaccines they may have received, including those given in nontraditional settings, such as health fairs or at the supermarket.

The initial focus of VAMPSS will be on the respiratory health of pregnant women, including asthma medications, seasonal and H1N1 influenza vaccines and antiviral medications used to prevent and treat influenza. Although there is no evidence to suggest that influenza vaccines pose any harm to pregnant women or their offspring, the newer and more comprehensive data provided by VAMPSS will improve understanding of the safety of these and other medications and vaccines that are taken during pregnancy. ❖

Research

Patients Lack Knowledge of Hospital Medications

A new study to assess patient awareness of medications prescribed during a hospital visit found that 44 percent of patients believed they were receiving a medication they were not, and 96 percent were unable to recall the name of at least one medication they had been prescribed during hospitalization.

The study, conducted at the University of Colorado, Denver, and published in the December 2009 issue of the *Journal of Hospital Medicine*, involved 50 participants between ages 21 and 89 who all self-identified as knowing their outpatient medications, spoke English and were from the community around the University of Colorado Hospital. Nursing home residents and patients with a history of dementia were excluded. Patients younger than 65 were unable to name 60 percent of medications that they could take as needed, whereas patients older than 65 were unable to name 88 percent of these medications. The difference remained even after adjustment for the number of medications.

Antibiotics were the most commonly omitted scheduled medication with 17 percent of all omitted drugs being from this medication group, followed by cardiovascular medications (16 percent) and antithrombotics (15 percent). Among medications that could be taken as needed, analgesics (33 percent) and gastrointestinal medications (29 percent) were commonly omitted by patient recall.

Inpatient medication errors represent an important safety issue, with one review finding some degree of error in almost one in every five medication doses. The patient, as the last link in the medication chain, represents the final individual capable of preventing an incorrect medication administration. ❖

Medicine

FDA Approves Drugs for HAE Treatment

The Food and Drug Administration (FDA) has approved two new drugs for the treatment of acute attacks of hereditary angioedema (HAE), a rare genetic disorder characterized by severe, debilitating and often painful swelling, which can occur in the abdomen, face, hands, feet and airway.

The first treatment, Berinert C1-Esterase Inhibitor by CSL Behring, was approved last October. The approval of Berinert was based on the results of the Phase II/III double-blind placebo-controlled International Multi-center Prospective Angioedema C1-Inhibitor Trial (IMPACT), which studied the efficacy and safety of C1-inhibitor concentrate.

The second treatment, Kalbitor by Dyax, was approved last December for patients 16 years of age and older. Kalbitor is a potent, selective and reversible plasma kallikrein inhibitor and the first subcutaneous HAE treatment approved in the U.S. As part of the approval, Dyax, together with the FDA, established a risk evaluation and mitigation strategy program to communicate the risk of anaphylaxis and the importance of distinguishing between a hypersensitivity reaction and HAE attack symptoms.

In January, CSL Behring launched its Berinert Expert Network (BEN), a full-service support program for healthcare providers and for HAE patients and their caregivers. BEN provides information and assistance in securing access to Berinert, insurance and reimbursement, educational resources and tools, and assurance and assistance. For more information about BEN, call (877) 236-4423. ❖

Vaccine Update

Novavax Inc.'s new **swine flu vaccine** that is produced using genetically engineered virus-like particles (rather than being grown inside chicken eggs like traditional flu vaccines) has prompted an immune response in patients during a mid-stage study. The company is currently conducting a larger, 3,500-person study of the vaccine, which can be grown in weeks instead of months using the traditional method.

GlaxoSmithKline PLC struck a deal with Intercell AG, an Austrian company, to develop vaccines delivered through a **patch**, a technology that health professionals hope could help expand the use of vaccines. The U.K.-based Glaxo will pay for access to the technology and marketing rights to patches used by travelers to guard against diarrhea and pandemic flu.

Giving a vaccine through a scratch on the skin (**scarification**) triggers a stronger immune response than injected vaccines, say researchers at Brigham and Women's Hospital, who also found that scarification requires 100 times less vaccine to prompt an immune response. Scarification was first used nearly two centuries ago to give the first smallpox vaccinations, but today, nearly all modern vaccines are given via injection. The study was published in the 17 issue of *Nature Medicine*.

The Food and Drug Administration approved a **high-dose influenza vaccine, Fluzone High-Dose,** for people 65 and older. The vaccine, which is produced by Sanofi Pasteur, was designed to produce a stronger immune response and better protect older adults against the seasonal flu. It will be available in the fall of 2010 in advance of the next flu season.

BiondVax Pharmaceuticals Ltd. of Israel has successfully completed the clinical phase of its second Phase I/II clinical trial of the company's Multimeric-001 **universal flu vaccine**. Initial results show that the vaccine is safe and well-tolerated, causing no severe or serious adverse events.

The FDA has approved Pfizer Inc.'s Prevnar 13 pneumococcal 13-valent conjugate vaccine. Prevnar 13 is indicated for active immunization of children 6 weeks through 5 years of age for the prevention of invasive disease caused by **13 Streptococcus pneumoniae**.

According to a new report from the Institute of Medicine, which identifies priority areas for updating the **National Vaccine Plan**, the U.S. lacks immunization protection against several serious illnesses. The revised plan should include a strategy to accelerate development of high-priority vaccines, and should emphasize the importance of expanding funding for safety research and monitoring. It also will include the development of a national communications strategy to clarify the importance

Research

Vaccine to Improve Immune System in Newborns

University of Missouri researchers are working on a vaccine to improve infants' immune systems, which are susceptible to diseases and infections such as jaundice and E. coli, right after birth. The researchers have identified a group of depleted white blood cells that might lead to an immune-strengthening vaccine.

Specifically, they have found that newborns have an imbalance of two different groups of T-helper cells (TH cells), which are white blood cells and the main fighters in the immune system. Newborns have a large amount of TH2 cells, a group of white blood cells that mediates allergic reactions, but not enough TH1 cells, a group of white blood cells that fights infections. Environmental factors also affect the imbalance of these two groups of T-helper cells. The first time newborns are exposed to an antigen (a foreign substance that illicits a response in the immune system), their white blood cells are balanced. But, the second time they are exposed to the antigen, they create too much of the TH2 cells and not enough of the TH1 cells. This imbalance is what leads to possible infection and allergic reaction.

"What's happening is that the TH2 cells are killing the TH1 cells, creating the imbalance," Christine Hoeman, doctoral student in the University of Missouri School of Medicine, explains. "Once we know more about the timeline of the imbalance, we can start to develop the vaccine, which would increase the levels of TH1 and would ideally be administered in newborns soon after they're born."

The research was published in both the *Journal of Environmental Medicine* and *Trends in Immunology*. ❖

of vaccines and bolster public confidence in the immunization system.

Scientists seeking to understand how to make an **AIDS** vaccine have found the cause of a major roadblock. Originally, scientists thought that B cells (one of the first lines of defense against infection) are simply not able to "see" the HIV virus. But, instead, researchers have now found that, in mice, plenty of early stage B cells are produced, but most are destroyed because the immune system sees them as a potential threat. Researchers plan on using this new mouse model to test ways to teach the immune system to enable the production of B cells containing a rare but potent, broadly neutralizing human antibody that is able to block HIV infection.

GlaxoSmithKline has launched a program in the U.S. to provide **free vaccines** to adults ages 19 and older who don't have health insurance and whose income totals no more than $27,075 for a single person or $36,425 for a couple. The program will cover low-income adults who meet eligibility requirements. The free vaccines include shots for hepatitis A and B, tetanus, diphtheria and whooping cough. The company's cervical cancer vaccine, Cervarix, also will be included for women between the ages of 19 and 25.

The FDA has approved the **human papillomavirus (HPV)** vaccine Cervarix for use in girls and young women ages 10 to 25 to help prevent cervical cancer. Manufactured by GlaxoSmithKline, Cervarix targets two HPV strains, HPV 16 and HPV 18, which are leading causes of cervical cancer.

The federal government in Canada has approved the **HPV** vaccine Gardasil for boys and men ages 9 through 26, the same age range as its approval in girls and women. The Public Health Agency of Canada is reviewing the data from studies of the vaccine and will make a recommendation to the provinces based on their findings.

A new vaccine shows promise for protecting young children from **malaria**. GlaxoSmithKline's vaccine, which uses an immune system blocker called an adjuvant, targets the malaria parasite as it is actively infecting red blood cells and causing fever and illness. This blood-stage vaccine acts at a later stage in the malaria parasite's life cycle than Glaxo's experimental vaccine Mosquirix.

The Vaccine Research Center at the National Institute of Allergy and Infectious Diseases has posted a new confidential screening form to help interested people determine if they are eligible to volunteer to participate in **clinical studies** of potentially life-saving vaccines. The form can be accessed at https://www3.niaid.nih.gov/Volunteer/volunteerEligibility.htm.

Safety

Google Accepts Only VIPPS-Accredited Ads

Google has refined its advertising model to accept advertisements only from online pharmacies in the U.S. that are accredited by the National Association of Boards of Pharmacy's Verified Internet Pharmacy Practice Sites (VIPPS) program. The change cuts out third-party verifiers, leaving VIPPS as Google's lone online pharmacy accreditation program for drug advertisers in the U.S.

The Partnership for Safe Medicines (PSM) has applauded Google's updated policy, noting that it is a step in the right direction. Tom Kubic, president of the Pharmaceutical Security Institute and PSM partner, is encouraging the other major providers of Internet search tools to follow Google's lead. "Clever criminals will quickly adapt to these changes and move to other search engines to peddle their unsafe medicines," says Kubic. "Only by adopting uniform, strict standards on paid advertising can we really protect unsuspecting patients." ❖

Research

High-Intensity Ultrasound to Treat Cancer

A new study has found that an intense form of ultrasound that shakes a tumor until its cells start to leak can launch an attack on cancer. Led by researchers at Duke University's Pratt School of Engineering, the study suggests that a high-intensity focused ultrasound (HIFU) can activate an "alarm" that enlists immune defenses against the cancerous invasion. These findings imply that once triggered by HIFU, the immune system might even search for and devastate cancer cells, including those that have spread through the bloodstream to lurk in other parts of the body.

HIFU is in use or testing in China, Europe and the U.S. to kill tumors by heating them. But, HIFU in its current form can be used to treat only the primary tumor. "In most cancers, what actually ends up killing the patient is the spread of the cancer from its original site to other parts of the body," explains Pei Zhong, an associate professor in Duke's mechanical engineering and materials science department. "If the patient has a tumor in the kidney or liver, several treatment options — including surgery, radiation and HIFU — can be used to get rid of the cancerous tissues. However, if the cancer cells spread to other vital organs such as the lung or brain, the outcomes are often much worse." Therefore, if HIFU is delivered in a different mode, with an emphasis on using mechanical vibration to break apart the tumor cells, it may have a more significant impact in suppressing cancer metastasis by waking up the immune system. ❖

Safety

IVIG Reduces Pain in CPRS Patients

Researchers at the University of Liverpool found that a dose of intravenous immunoglobulin (IVIG) significantly reduced pain in almost half of patients with complex regional pain syndrome (CPRS), an unexplained chronic condition that can develop after an injury to, or loss of, a limb.

The researchers, whose study was published in the *Annals of Internal Medicine*, gave a single low-dose transfusion of IVIG to 13 volunteers with pain syndrome and found it significantly eased the pain in just under 50 percent of them. The pain relief lasted five weeks on average, and the treatment had few adverse side effects. And, while the patients in the study were given a single, low-dose infusion, in the future, treatment could consist of higher doses and be repeated to give extra benefits. "The discovery is expected to have a real impact on the treatment of other unexplained chronic pain conditions," says Andreas Goebel, an expert in pain medicine who led the study. "If one pain condition can be effectively treated with an immune drug, then it is possible that other types will also respond." ❖

Did You Know?

"One of the most common and most dangerous medication errors people can make is to accidentally overdose on acetaminophen (Tylenol) or ibuprofen (Advil, Motrin) by taking both the painkiller and an over-the-counter cold and flu remedy that also contains it."

— Caring.com

Research

Blood Test Developed for Alzheimer's

A diagnostic blood test for Alzheimer's disease has been developed by OPKO Health Inc. The test, designed to detect elevated levels of antibodies unique to the disease, was approximately 95 percent accurate in initial testing. The test could be helpful in identifying patients for clinical trials for new Alzheimer's drugs, as well as to confirm the diagnosis in a clinical setting.

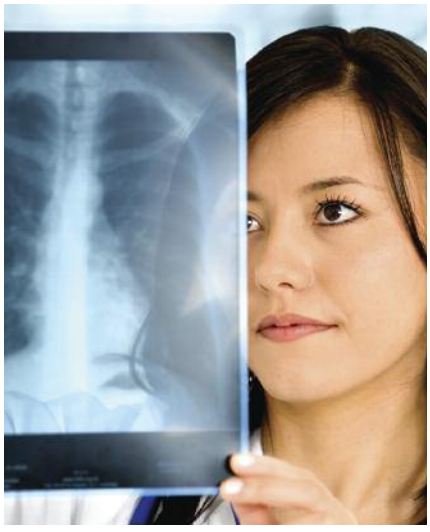
The novel Alzheimer's disease-specific antibodies were discovered using a proprietary platform being developed by OPKO that appears to be capable of identifying such biomarkers for any disease to which the immune system reacts, including cancer, autoimmune disease, neurodegenerative and infectious diseases. Additional studies required for regulatory approval and commercial use will be performed by OPKO. ❖

Research

H1N1 Deaths and Autoimmunity?

Individuals who develop serious pneumonia from H1N1 infection may have an autoimmune disorder, according to a study reported on in the Dec. 15, 2009, edition of *Newswise*. According to the study, the overproduction of the immune system component interleukin-17 may be responsible for serious illness and even death. Patients who were hospitalized with H1N1 were found to have elevated levels of interleukin-17, a substance that can cause an excess number of white blood cells to respond to lung injury caused by the H1N1 virus, which results in increased inflammation in the lungs.

"In rare instances, the virus causes lung infections requiring patients to be treated in hospital. By targeting or blocking TH17 (interleukin-17) in the future, we could potentially reduce the amount of inflammation in the lungs and speed up recovery," says Dr. David Kelvin, head of the study in Canada.



Study authors say that possible future interventions could include a blood test to identify those who are at high risk of developing autoimmunity in the case of H1N1 infection and potentially using drugs to regulate interleukin-17. ❖

Safety

Low IgG Levels Linked to Severe Flu

Australian researchers specializing in infectious diseases found that pregnant women who became severely ill with the H1N1 flu had low levels of IgG to help fight off the virus and help the body respond to vaccine. On the other hand, moderately ill pregnant women were much less likely to have significantly suppressed levels of the antibody.

The researchers tested patients for antibody levels and found that patients who needed ICU were IgG2 deficient. Severe cases had IgG2 levels that were about one-third of those detected in people who were moderately ill. Three of four critically ill patients treated with immune globulin survived. While the testing was performed only in pregnant women, the scientists believe that the deficiency might explain why a small subset of swine flu cases become gravely ill, while most people suffer through only a bout of the flu. The study was conducted at Austin Health, a network of three hospitals in Melbourne, and because the testing involved a small number of people, further study is needed. ❖

Market Report

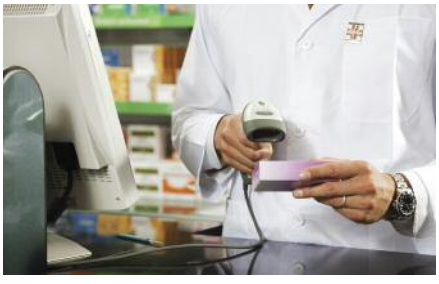
Coagulation Factor R&D Report Published

A new report, titled *Coagulation Factors 2009: Target Pipeline and Corporate Benchmark Analysis*, analyzes and assesses the target pipeline for each of the coagulation factors used for systemic and topical administration. Companies active in the therapeutic coagulation business are evaluated, and the strengths, weaknesses, opportunities and threats in their R&D pipeline are benchmarked in the respective peer group. Technologies used for creation of next generation coagulation factors also are discussed. More information about the report is available from Research and Markets at www.research and markets. com/research/384161/coagulation_factor. ❖

Reimbursement FAQs

Some commonly held misunderstandings about vaccine reimbursement are clarified.

As an independent pharmacy, I would like to provide vaccines for my customers, but the overhead risks are too high. Is there a way to avoid these risks?



Yes. A pharmacy operator's best solution is to work with a vaccine provider that can remove the risks associated with vaccination, such as purchasing expensive products and storing them in inventory until they are used. Some vaccine providers allow the consumer to register online to receive a vaccine and then will send the vaccine specific for that consumer to the pharmacy "just in time" for administration. A vaccine provider also will provide billing services and pay the pharmacy to perform the administration. This type of partnership allows independent pharmacies to provide vaccination services to their community without taking costly overhead risks.

Medicare Part B covers 100 percent of the cost for some seniors' vaccines. How well is this benefit used?

According to the Centers for Medicare and Medicaid Services (CMS), pneumonia and influenza are the eighth leading cause of deaths in older adults. Medicare Part B pays for one influenza vaccine each year with no copayment or deductible applied. Medicare generally pays for one pneumonia vaccination for all Medicare beneficiaries per lifetime. However, if a beneficiary is considered high risk, a booster may be given and also is covered in full.

Despite full coverage for these vaccines, rates of immunization in the senior population remain suboptimal, particularly in minority populations. This may be due in part to lack of education about Medicare benefits. Moreover, from a reimbursement viewpoint, the problem is likely due to access issues on multiple levels.

For instance, providers are unable to bill Medicare for an office visit when the only reason for the visit is a vaccine. If the office visit is for a medical reason covered under Medicare, the vaccine given in conjunction with that visit will be covered. Consequently, seniors simply needing a vaccine may put off vaccination until they have another reason to visit their physician. In addition, some Medicare Advantage plans limit the number of contracted providers for their Medicare members, thus eliminating some of the more convenient vaccine locations such as supermarket pharmacies.

To learn more about provider resources for vaccines, go to www.cms. gov/Adult Immunizations/02_Provider resources. asp.

Is Gardasil covered by insurance?

Insurance companies are more likely to cover vaccines that the Centers for Disease Control and Prevention (CDC) recommend. HPV vaccines, such as Gardasil, are recommended by the CDC for both females and males.

How do insurers reimburse for vaccines?

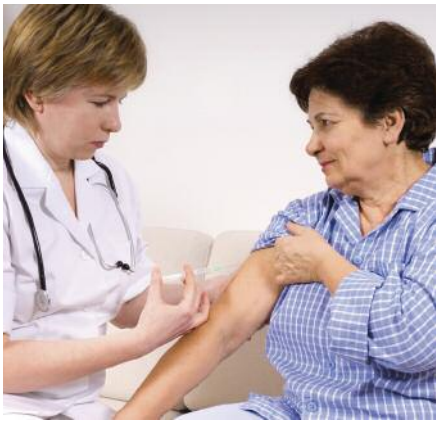
Insurers often see the value of vaccines, and many provide vaccine coverage. Depending on the insurer, vaccines may be covered under the wellness benefit, major medical or the prescription plan. Wellness benefits generally cover 100 percent of the vaccine with no out-of-pocket expense for the patient.

However, vaccines may be subject to copayments and deductibles in some plans. For some providers, the cost of filing reimbursement claims outweighs the benefits. In this case, filing for reimbursement may be left up to the patient. Recently passed healthcare reform may change how vaccines are covered by January 2011.

According to the Kaiser Family Foundation's Summary of Health Reform, plans will be required to provide, at a minimum, coverage without cost-sharing for preventive services rated A or B by the U.S. Preventive Services Task Force (USPSTF). This reform would include vaccines.

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.

As a specialty pharmacy, we would like to expand our services to offer flu vaccine clinics for employer groups. Targeting large employers seems to make the most business sense for us. However, most large employers already contribute to their employees' health insurance, which usually covers vaccines. Why, then, would these employers be willing to fund and host a vaccine clinic if vaccines are already a covered insurance benefit?



According to the U.S. Chamber of Commerce, flu outbreaks cost the U.S. economy $10 billion in lost productivity and medical expenses annually. Working to reduce these costs, employer-sponsored workplace flu clinics have proven to keep employees healthy and working. Vaccinations not only decrease the loss of productivity related to absenteeism, but workers protected by vaccination decrease the risk of infecting co-workers, halting the potential spread of disease. Because workplace flu shot clinics are so quick and easy, they can be held during any shift and are completed in as little as five to 10 minutes per employee. Providing quick, convenient vaccine access to employees boosts the rate of vaccination in the workplace, decreases the risk of infection, and thereby supports productivity and, ultimately, profits, always key concerns for employers. To learn more about employer-sponsored vaccination clinics, go to www.VaxAmerica.com. ❖

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

Ask Our Experts

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

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

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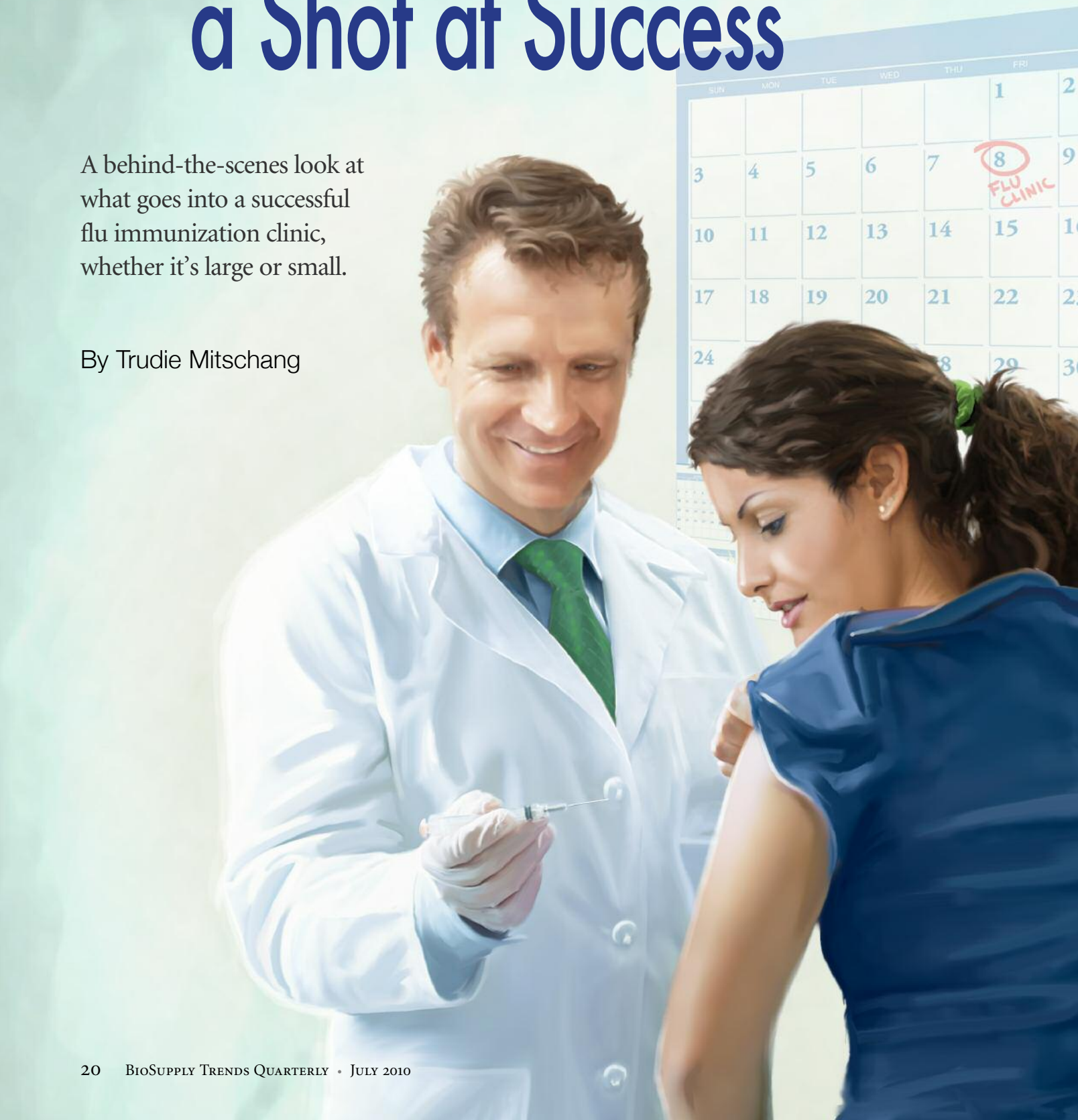
Giving Your Flu Clinic a Shot at Success

A behind-the-scenes look at what goes into a successful flu immunization clinic, whether it's large or small.

By Trudie Mitschang



Anyone who has ever hosted a public flu immunization clinic can attest that there is a lot more that goes into a successful event than meets the eye. At a glance, you might think all you need to do is order vaccine, locate an administration site, hang out some signs and posters, and start immunizing. In truth, planning a large flu clinic is not unlike planning a party or corporate event, and the devil is always in the details.

Of course, not every flu clinic is large enough to need lengthy advanced planning. Many clinics are small-scale events within a private practice or local pharmacy, with a steady and manageable flow of foot traffic. Still, it's a good idea to follow most of the guidelines that apply to a larger clinic, scaling down recommendations to meet your individual needs. For example, while crowd management may not be a concern, providing adequate seating is important if you expect lots of seniors. Similarly, marketing your clinic and getting the word out to the community is an important step no matter how many people you anticipate.

According to the Centers for Disease Control and Prevention (CDC), to facilitate the most efficient and safe delivery of flu vaccine via a community clinic, a number of key areas must be addressed: leadership, human resources, location, clinic specifications, crowd management, security and advertising.

Leading the Way

Identifying leaders for your vaccination campaign is essential. A point person can help manage staff, delegate duties and deal with minor problems as they arise on the day of the event. In addition to a clinic manager, the CDC recommends designating team leaders for supplies, logistics, medical personnel and support functions.

Promoting Team Spirit

Just how many people does it take to run a flu clinic? That depends on the size of the clinic, but in general, plan to have staff to act as greeters, screeners, registration personnel, payment collectors, traffic flow controllers, vaccination administrators and assistants, and security and emergency medical personnel. Obviously, some of these roles will overlap. In the case of a smaller clinic, you may need only registration personnel and vaccine administrators. No matter how many patients you expect to see, be sure to employ multilingual staff to meet your community's needs.

In terms of staff training, start early. Weeks before the clinic date, plan to host training sessions to prepare personnel and answer questions. For smaller clinics, be sure to meet at least twice prior to the day of the event to review logistics and ensure all staff members are clear on their individual roles. It's also a good idea to cross-train; having people prepared to jump in as needed will keep things running smoothly when things don't go as planned. Last, avoid staff burnout by pre-scheduling time for breaks and snacks in a designated area.

Location Really Is Everything

When it comes to finding an appropriate site for a large clinic, locations that typically work well include school gyms, churches, auditoriums, theaters or other large covered public spaces accessible to the elderly and persons with disabilities.

Other key considerations include ensuring proximity to mass transit, ample parking, separate entry and exit doors, adequate lighting, functional and accessible restrooms, and adequate space for all clinic functions such as screening, registration, vaccine storage, vaccination and staff breaks. In addition, select a facility with space for reasonably large and well-delineated covered gathering areas outside and inside of the clinic.

No matter what time your flu clinic is scheduled to start, expect people to show up early.

Keeping Things Moving

The logistics of a large flu clinic involve identifying the various stations an individual will need to visit as they make their way through the facility. Use ample amounts of rope and signs in multiple languages to delineate routes and manage traffic flow. Since you should anticipate lines, provide seating near the various stations. Privacy screens may also provide discretion for those who need to partially disrobe to be vaccinated. Additionally, you may want to section off a private area where clients who experience adverse reactions following vaccination can be evaluated and treated.

Small flu clinics will not be concerned with crowd control, but should plan for an ebb and flow of patients during clinic hours. If you are expecting a high turnout during certain times of the day, like lunch hours, be sure to have ample seating available should there be a longer-than-expected wait.

Crowd Management 101

No matter what time your flu clinic is scheduled to start, expect people to show up early. Have staff arrive one to two hours before clinic start time to welcome and screen clients,

even if pre-scheduling is being used. Other helpful tips from the CDC include:

- Arrange accommodations for special-needs clients, such as those with disabilities, for expedited access into the clinic.
- Direct arriving clients into several lines, and use numerous signs and announcements to clarify who falls into high-risk groups.
- Communicate the number of vaccine doses available.
- Update clients on their estimated waiting times.
- If vaccine is being prioritized for certain groups, inform waiting clients that high-risk populations will be served first.
- Schedule at least two screeners per line to reduce crowd size and waiting times.

Once clients are inside:

- Have staff assist as needed with consent forms and/or vaccination cards.
- Utilize runners to keep staff stocked with ample supplies.
- Maintain a steady flow of clients through the clinic so that vaccinators are never without a client at their stations.
- Have clearly marked exit doors to keep the traffic moving and avoid bottlenecks.

Helpful Hints from a National Flu Shot Provider

VaxAmerica is a company on the frontline when it comes to planning and implementing flu vaccine clinics. A program of NuFACTOR, FFF Enterprises' specialty pharmacy, VaxAmerica was launched in 2008, and since then the company has been blazing new trails when it comes to making flu vaccination fast, affordable and convenient. Last year, it hosted its own series of H1N1 flu clinics, vaccinating nearly 4,000 men, women and children. According to Nancy Creadon, vice president of VaxAmerica Inc., some key components of a successful flu clinic include:

- Book early: Quarter one is the best time to book your clinic for the fall. Less lead time results in issues with staffing and vaccine supply.
- Engage participants months before the clinic date by providing information about the benefits of the vaccine.
- Provide incentives to get people to receive their flu shots. Employers may provide lunch coupons. Colleges could provide a postcard to send home to mom and dad letting them know their students got their shot. And everyone likes coupons for free fast-food meals. There are so many creative ideas to reach people. It is a small investment with large returns.
- Utilize the posters and materials provided by your flu shot provider.
- Provide clear direction regarding the location, date and time of your clinic weeks in advance so people can mark their calendars.
- Make sure you have a functional landline phone at the location in the event of an emergency. Sometimes cell coverage is unreliable in a medical emergency.
- Provide clipboards and pens so necessary documentation can be completed easily.
- Make sure your vaccine provider gives consumers a receipt of vaccination.

Safety First: Maintaining Clinic Security

Security may be an overlooked area of concern. To ensure adequate protection in the clinic, require all staff to wear identification cards color-coded for their job functions. Utilizing a uniformed presence to act as security and assist in managing crowds also can be helpful. Make sure to secure the vaccine and protect clinic staff and their valuables. Be sure to discard any vaccine-filled syringes remaining after the clinic closes. And, consider recruiting local volunteers familiar to clinic customers since they may be especially effective in diffusing crowd-related tension.

Small flu clinics will not be concerned with crowd control, but should plan for an ebb and flow of patients during clinic hours.

Getting the Word Out

Getting people to attend your flu clinic requires advanced planning and ample promotion. Use multilingual and multimedia channels, and if pre-scheduling, provide clear instructions for how to set up appointments via telephone, in person or online. Remember that part of your promotion is educational not just informational; many people still need to be convinced that flu shots are necessary and safe, so use appropriate messaging to reach these population groups.

Planning Well In Advance

With proper forethought and planning, a successful flu vaccination clinic can be staged if key elements are addressed well in advance. Following tried-and-true preparation guidelines maximizes the effectiveness and efficiency of flu clinics, resulting in increased protection for the community. ❖

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

Shot of the Future:
Trends in Therapeutic Vaccines

Vaccines to treat pre-existing conditions have the potential to radically change medical treatment. And, while they have been in the pipeline for years, recently there's renewed hope that therapeutic vaccines might soon be available to treat various diseases.

By Ronale Tucker Rhodes, MS

It is said that "an ounce of prevention is worth a pound of cure." But, when it comes to many diseases, prevention is simply not an option — or at least not in the near future. Despite great strides in the development of preventive vaccines, they may simply be unlikely or impossible for diseases such as cancer, HIV, Alzheimer's and others. On the other hand, a therapeutic vaccine could be more feasible. Indeed, millions of individuals who have already contracted a disease are in need of a vaccine to treat them. "There are some diseases, like Alzheimer's, that we just don't have a clue how to prevent with a vaccine," says Hildegund C.J. Ertl, MD, program leader in the immunology program at the Wistar Institute at the University of Pennsylvania. "But, in the future, therapeutic vaccines could be crucial for diseases that we learn how to treat but not prevent."[1]

History of Therapeutic Vaccines

Manufacturers have long been working to bring therapeutic vaccines to market. Yet, despite clinical trials showing remarkable improvements in selected small populations, very few have gained regulatory approval. Outside of the U.S. market, vaccines that have gained approval include Avax Technologies' M-Vax (for melanoma), Intracel's OncoVax (for colon cancer) and Corixa's Melacine (for late-stage melanoma). However, each has been marketed in a very small number of countries, and their success has been limited by efficacy, high cost and low acceptance of unproven therapeutic vaccines among physicians.[2]

To date, only three vaccines have gained regulatory approval in the U.S. One vaccine, Provenge, was just recently approved

by the Food and Drug Administration (FDA) at the end of April. Dendreon Corp.'s Provenge is a first-of-a-kind prostate cancer treatment that uses the body's immune system to fight the disease. It is intended to treat cancer that has spread elsewhere in the body and is not responding to hormone therapy. Provenge is made by taking immune cells from a patient's blood and exposing them to a protein found in most prostate cancers, which then encourages the cells to attack the cancer.[3]

...therapeutic vaccines are intended to treat already existing diseases by strengthening the body's natural defenses against them.

A second vaccine is Teva Pharmaceutical's Copolymer 1, used to treat multiple sclerosis, which was approved by the FDA in 2003. The third is Merck & Co.'s Zostavax vaccine for the treatment of shingles, also approved by the FDA in 2003. While Zostavax may be considered by some to be a preventive vaccine, according to Dr. Martin G. Myers, MD, executive director of the National Network for Immunization, "Zoster is a therapeutic vaccine because [those individuals] are already infected with the virus and [the vaccine] is altering the immune response to the virus. [The vaccine] both reduces the likelihood that the person is going to develop shingles and reduces the recurrence of the disease they got many years ago."

Vaccines, then, such as Provenge, Zostavax and Copolymer 1 are an advancement in healthcare that could lead the way for other therapeutic disease intervention. And now, due to even greater scientific advances, a new wave of therapeutic vaccines may turn the tide. According to a 2006 report from independent market analyst Datamonitor, therapeutic vaccine development is currently heavily weighted toward cancer vaccines, which then accounted for 60.6 percent of all active pipeline projects. In addition, there is greater interest by manufacturers in providing therapeutic vaccines for HIV, Alzheimer's, nicotine and drug addiction, as well as allergic, central nervous system and cardiovascular diseases.[2]

What Are Therapeutic Vaccines?

Vaccines boost the immune system's natural ability to protect the body against foreign invaders known as microbes that can cause disease. Microbes carry antigens that "tell" the immune system they are foreign, and therefore should destroy them and remember them to prevent another infection. Microbes used in traditional vaccines are usually killed or weakened so they don't cause disease, but are able to stimulate an immune response.[4]

While preventive (or prophylactic) vaccines are intended to prevent diseases from developing, therapeutic vaccines are intended to treat already existing diseases by strengthening the body's natural defenses against them. For instance, the goal of therapeutic cancer vaccines is to stop cancer cell growth, cause tumor shrinkage, prevent cancer from coming back, or eliminate cancer cells that are not killed by other forms of treatment, such as surgery, radiation therapy or chemotherapy.[4]

But, diseases such as cancer and HIV pose an interesting problem for scientists developing therapeutic vaccines. The immune system doesn't easily recognize the threat posed by an already growing cancer because cancer cells carry normal self antigens in addition to any cancer-associated antigens. Cancer cells also sometimes undergo genetic changes that lead to the loss of cancer-associated antigens, and they can produce chemical messages that suppress specific anti-cancer immune responses, thus managing to escape a strong attack.[2] On the other hand, other viruses such as HIV can overwhelm the immune system and shut it down before it can work.[1]

The Makings of Therapeutic Vaccines

There are two basic types of therapeutic vaccines. Patient-specific (personalized or autologous) vaccines are created using the patient's own tissue. Non-patient-specific (generalized or allogeneic) vaccines are made with off-the-shelf, mass-produced therapies.[2]

The first therapeutic vaccines developed were mainly personalized vaccines. But, while personalized vaccines offer advantages to patients due to their efficacy and specificity and don't require an in-depth understanding of the exact antigens involved, they pose many problems, including a very high cost, low scalability of manufacture, concerns over sterility and a more complex regulatory approval process. Therefore, generalized vaccines now dominate the research pipeline.[2]

Some specific types of therapeutic vaccines being developed include antigen vaccines, which provoke the immune system to create an antibody to fight the antigen; dendritic cell vaccines, which grab foreign germs and bring them to other immune cells that create antibodies to attack them; DNA vaccines, in which bits of DNA are injected into cells to instruct the immune system to keep revved up and alert; and tumor cell vaccines, which use actual cancer cells that are removed during surgery, killed or tweaked in some way and then introduced back into the body to trigger an immune response. These vaccines can be either patient-specific or non-patient-specific.[1]

An increasing trend in therapeutic vaccines is the use of multiple antigens and adjuvants to attack microbes from multiple angles.[2] Because antigens and other substances are often not enough to make effective treatment vaccines, researchers are adding ingredients, known as adjuvants, which boost immune responses that have been set in motion by exposure to antigens or other means.[4]

Vaccines Currently Being Studied

While therapeutic vaccines are being studied for a host of diseases, the three most promising appear to be cancer, HIV and Alzheimer's.

Cancer. Dozens of vaccines are being tested for various types of cancer, including breast, colorectal, kidney, leukemia, lung, lymphoma, melanoma, ovarian, prostate, pancreatic and others. British researchers have developed a vaccine that can be used to stop acute myeloid leukemia (AML), the most common form of cancer in adults, from returning after chemotherapy or bone marrow transplant. Once a patient has been diagnosed, the vaccine prompts the immune system to hunt down cancer cells and destroy them. To prevent a relapse, the vaccine then prompts the immune system to recognize leukemia cells if they return. The first clinical trial of the vaccine was held in early 2010 at King's College London. The research will be published in the *Journal of Cancer Immunology, Immunotherapy*.[5]

Like Dendreon's Provenge, another pancreatic cancer treatment vaccine in trials is the GVAX Precreas vaccine, which has received orphan drug status from the FDA. BioSante Pharmaceuticals, which manufactures the vaccine, also is conducting clinical trials to measure the vaccine against other cancers, including leukemia and breast cancer.[6]

Researchers in the Netherlands have created a dendritic cell-based vaccine against mesothelioma, a rare form of cancer typically affecting the lining of the lungs, and primarily caused by exposure to airborne asbestos fibers. The researchers tested the vaccine in 10 patients and achieved 80 percent effectiveness.[7]

In November 2009, researchers reported on a trial of a vaccine against the most common type of human papillomavirus, HPV-16. They investigated the immunogenicity and efficacy of a synthetic long-peptide vaccine in 20 women with HPV-16-positive, high-grade vulvar intraepithelial neoplasia. Three months after the last vaccination, 12 of 20 patients had clinical responses and reported relief of symptoms. Five women had complete regression of the lesions and HPV-16 was no longer detectable in four of them. At 12 months of follow-up, 15 of 19 patients had clinical responses, with a complete response in nine of 19 patients, and the complete response rate was maintained at 24 months of follow-up.[8]

While therapeutic vaccines are being studied for a host of diseases, the three most promising appear to be cancer, HIV and Alzheimer's.

Most recently, a Phase I clinical trial tested the safety and immunogenicity in women with a previous history of cervical intraepithelial neoplasia 2/3, a precursor lesion prior to the development of cancer. The vaccine, VGX-3100 by Inovio Biomedical Corp., targets the E6 and E7 proteins of HPV types 16 and 18, and has shown strong specific antibody responses to tumor antigens.[9]

HIV. For decades, researchers have been looking for a therapeutic vaccine for HIV. The earliest study, the STEP Study, tested an Adeno 5 (adenovirus type 5) vaccine candidate in the U.S., Latin America and Australia. However, because the study did not lower the viral load among those infected, the study was stopped.

In a newer study, researchers loaded dendritic cells with killed AIDS viruses and then injected them back into the person, which triggered an effective immune response. In the

2004 study of 18 people injected with the vaccine, the amount of virus in the blood dropped by 80 percent. After one year, eight of the people still had a 90 percent drop in their viral levels.[1]

New and encouraging results from pre-clinical research by Bionor Immuno AS will move the therapeutic and potentially preventive HIV vaccine candidate Vacc-C5 into a Phase I/II clinical trial. The research results indicate that Vacc-C5 may induce a protective antibody response in HIV patients similar to that found in patients with slow or non-progressing disease.[10]

Most recently, GeoVax Labs Inc., a Smyrna, Ga.-based biotechnology company that creates and tests HIV/AIDS vaccines, has been granted federal permission to begin a Phase I clinical trial for a treatment for people infected with HIV. The trial will monitor safety while evaluating the ability of the vaccine to elicit protective immune responses in vaccinated participants.[11]

Currently, two Phase II and one Phase III clinical trials are in progress. See the article, Update on HIV, on page 44 of this issue.

Alzheimer's. Existing drugs for Alzheimer's can delay the progress of disease symptoms, but because their effect wears off relatively quickly, the disease is allowed to take its devastating course. However, several new therapeutic vaccines being studied could actually stop the disease in its tracks. The most promising is known as CAD106, a collaboration program between Novartis Pharma AG and Cytos Biotechnology. It is an experimental vaccine that may help the immune system attack a protein that plays a key role in the illness, thus slowing down its progress.

Early tests of CAD106 showed that the vaccine is highly effective at breaking up the sticky protein that clogs the brain in Alzheimer's patients and destroys vital connections between brain cells.[12] While a study of the vaccine was suspended in 2002 after 6 percent of subjects developed brain inflammation, a year later, researchers tracked the people who received the vaccines and found that approximately 20 percent of them were making antibodies to the protein, meaning their immune system was attacking it. In addition, the group scored slightly better on memory tests than people who had not received the vaccine.[4] Different versions of the vaccine are still being studied, and a Phase II clinical trial is currently in progress.

Other therapeutic vaccines. The search for therapeutic vaccines is expanding to a host of other diseases. Great effort is being devoted to developing therapeutic vaccines against tumors, hepatitis B, tuberculosis (TB), malaria, diabetes, high blood pressure and, possibly, against the bacteria that cause gastric ulcers. Copolymer 1 (also known as glatiramer acetate), used today as a therapeutic vaccine against multiple sclerosis, "could lead to therapeutic vaccines against other autoimmune diseases such as myasthenia gravis, systemic lupus erythematosus and rheumatoid arthritis," according to an article published by the Proceedings of the National Academy of Sciences of the United States of America. "Furthermore, current studies raise hope for vaccines against prion diseases, bovine spongiform encephalitis and Creutzfeldt–Jakob disease."[13]

Another potential therapeutic vaccine being studied also may be applicable to other autoimmune diseases, according to a study published in the April 8 online version of the journal *Immunity*. Canadian researchers have successfully reversed type 1 diabetes in mice using a nanotechnology-based vaccine that appears to target solely the immune system cells responsible for the disease. Type 1 diabetes is an autoimmune disease, just like multiple sclerosis and rheumatoid arthritis, which are caused by an overactive immune system.[14]

Just recently, the Aeras Global TB Vaccine Foundation and the Dutch biopharmaceutical company Crucell N.V. announced the start of a Phase II clinical trial of the jointly developed TB vaccine candidate AERAS-402/Crucell Ad35 in HIV-infected adults. Earlier trials begun in 2004 support the immunogenicity and acceptable safety profile of the TB vaccine candidate at all dose levels.[15]

Therapeutic vaccines for addiction also are showing promise. Scientists may have created a new vaccine against cocaine addiction. The series of shots changes the body's chemistry so that the drug can't enter the brain and provide a high. The vaccine, called TA-CD, shows promise but also could be dangerous. Some of the addicts participating in a

study of the vaccine started doing massive amounts of cocaine in hopes of overcoming the vaccine's effectiveness. The study was published in the *Archives of General Psychiatry* in October.[16]

And, Nabi Biopharmaceuticals is partnering with GlaxoSmithKline to develop an anti-smoking vaccine, NicVAX, which will train the immune system to produce antibodies that attach themselves to nicotine. Once the antibodies are stuck to the nicotine, they will not be able to reach the brain, thus blocking the pleasurable effects of the drug. Nabi is currently in the late stages of the clinical study, and if testing is successful, GlaxoSmithKline will be responsible for getting the drug approved and bringing it to market.[17]

Therapeutic Vaccines: More Hope on the Horizon?

While some researchers believe that a host of therapeutic vaccines will likely become reality within the next 10 years, others are much more skeptical. The former say they likely will be because of the amount of research that is aimed at better understanding basic biology, as well as the technologies being created as part of this effort. "There are so many exciting new technologies and new understandings of diseases that have occurred in recent years," says Myers. "I think the potential for therapeutics is very large."

But, the latter say that while therapeutic vaccines seem to be on the horizon, they've seemed that way for a long time. "I remember when therapeutic vaccines were first developed for skin cancer in the 1960s," says Richard L. Wasserman, MD, PhD, clinical professor in the Department of Pediatrics at the University of Texas Southwestern Medical School in Dallas. "But 40 years later, we still don't have one."[1]

Canadian researchers have successfully reversed type 1 diabetes in mice using a nanotechnology-based vaccine that appears to target solely the immune system cells responsible for the disease.

But, it's possible that those delays are now over. "The real revolution of information occurred with the Internet and with microprocessing and so on, and the biologic sciences are just catching up," explains Myers. "All of these extraordinary technologies are just becoming available about the basic understanding of the disease process, and the amount of information that is being accumulated is remarkable." The average rule of thumb for bringing a vaccine to market "is seven to 10 years from proof of concept [showing that a vaccine is likely] to the end of Phase III trials," adds Myers. "And, it varies significantly with a new vaccine and a vaccine concept." ❖

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Vaccination Education:

2009 H1N1 Lessons Learned

From identifying the strain to prioritizing high-risk recipients, a look at lessons learned from the development and distribution of the H1N1 vaccine.

By Trudie Mitschang

From a public health perspective, there are many insights to be gleaned from the H1N1 pandemic of 2009-10, especially from the development, distribution and administration of the 2009 H1N1 vaccine. While the global impact of the disease was less dire than predicted, more than 17,000 deaths eventually were attributed to H1N1.[1] Amid early stages of panic, public demand for a vaccine was high, but when manufacturing delays caused delivery shortages, initial anger turned to apathy as many people shunned the vaccine when it finally arrived. Was it a case of too little too late? And what could have been done differently to get the vaccine distributed more efficiently?

An Unpredictable Outbreak

From the start, the 2009 H1N1 pandemic did not conform to prior assumptions. For one thing, it began in Mexico, not Asia, which was the anticipated origin of the next influenza pandemic. Second, it was not as deadly as health experts feared (although in the end, it was more communicable than expected, infecting 1,483,520 people worldwide).[2] Additionally, H1N1 did not follow previous outbreak patterns for influenza, showing up in the spring rather than the typical late fall, catching many public health officials off guard.

Once it surfaced, H1N1 gained notoriety and momentum rapidly, with the most serious and deadly cases noted in otherwise healthy young adults and children, compared with the seniors and infants who typically succumb to seasonal flu complications. It wasn't long before panic ensued as H1N1 cases spread from state to state and country to country. As the outbreak escalated to pandemic status, the world waited eagerly for word of a vaccine, and everyone from the World Health Organization (WHO) to the Centers for Disease Control and Prevention (CDC) rallied to inform and educate a frightened public about the next steps.

Because the virus was discovered early in humans, response was swift — the virus was characterized, tests were developed

and findings were shared at record speed. Vaccine manufacturers collaborated and it was "all systems go" in terms of vaccine development. Confidence was high that a vaccine could be delivered prior to the anticipated flu surge in late fall. In fact, the CDC expected to vaccinate more than half the U.S. population quickly. Health and Human Services Secretary Kathleen Sebelius was quoted as saying, "250 million vaccines have been ordered, and any American who wants to be vaccinated will be able to get a flu shot."

Unfortunately, things did not go exactly as planned.

Vaccine Production Methods Come Under Scrutiny

While new, streamlined flu vaccine manufacturing techniques were already under development when the 2009 H1N1 hit, none were far enough along to help with a pandemic of this magnitude. As a result, the 2009 H1N1 flu vaccine was produced using fertilized chicken eggs, a method used since the 1930s. The process involves drilling a hole into the eggshell so the virus can be injected into the amniotic cavity (the amniotic cavity provides a sterile and nutrient-rich environment for the influenza virus to replicate). Thereafter, the viruses are recovered by removing the amniotic fluid, which is then used to make the vaccine. At least that's how it's supposed to work. True to its unpredictable nature, the H1N1 flu virus did not grow as well as expected in eggs, apparently requiring different conditions to thrive than its seasonal counterpart. As a result, vaccine manufacturers had trouble growing enough of the virus to make the vaccines. Further complicating matters, pharmaceutical companies were producing vaccines for the seasonal flu and 2009 H1N1 at the same time, slowing production timelines even further. Amanda Gardner of *U.S. News and World Report* stated, "The H1N1 virus did not grow as quickly as expected during a half-century-old — and often-criticized — egg-based production technique used by pharmaceutical companies to make selected vaccines."[3]

As delays ensued, concerns about the dated manufacturing process came to light. "Eggs can be very cumbersome to work with," said John Treanor, MD, the flu expert at the University of Rochester Medical Center. "When you need hundreds of millions of fertilized eggs, you're dealing with a whole host of agricultural issues, as well as scientific concerns regarding the flu virus itself. Flu viruses can be temperamental, and it's not always an easy matter to get the virus to grow as you want in eggs."[4]

H1N1 gained notoriety and momentum rapidly, with the most serious and deadly cases noted in otherwise healthy young adults and children, compared with the seniors and infants who typically succumb to seasonal flu complications.

Overpromised and Underdelivered

The CDC initially told its Advisory Committee on Immunization Practices in late July that it hoped to have 120 million doses of vaccine for the novel influenza A (H1N1) virus available by October 2009. Unfortunately, the unexpected manufacturing issues made that a difficult promise to keep, and by August, federal officials expected only about 45 million doses to be available by mid-October. In actuality, barely 13 million doses arrived, creating frustration among health practitioners and the general public as supplies were rationed for high-risk patients.

Cell-Based Production: The Future of Vaccines

For decades, vaccines have been produced in chicken eggs. Now, a new technology using cell-based vaccine production could save hundreds of thousands of lives in the event of an outbreak of pandemic influenza, or some other infectious disease.[7]

In place of eggs, cell-based vaccine production utilizes laboratory-grown cell lines that are capable of hosting a growing virus. The virus is injected into the cells, where it multiplies. The cells' outer walls are then removed, harvested, purified and inactivated. Using this method, a vaccine can be produced in a matter of weeks rather than months. Other advantages include:

- Cell lines can be safely frozen indefinitely, increasing the capability to rapidly produce vaccines in the event of a pandemic.
- Cell-based vaccine production dramatically reduces the possibility for contamination and promises to be more reliable, flexible and expandable than egg-based methods.
- Vaccine manufacturers are able to bypass the steps needed to adapt the virus strains to grow in eggs.
- People allergic to eggs will be able to be immunized with a cell-based vaccine.

In May 2006, the Department of Health and Human Services awarded five contracts totaling more than $1 billion to accelerate development and production of new technologies for influenza vaccines within the U.S. These five contracts support the advanced development of cell-based production technologies for influenza vaccines and will help to modernize and strengthen the nation's influenza vaccine production methods. In March 2010, the U.S. Food and Drug Administration issued final guidance to help manufacturers who are developing safe and effective cell-based viral vaccines to better address emerging and pandemic threats.

For more information about cell-based vaccine production, see the article, Scientists Flying the Coop on Flu Vaccine Manufacturing, in the January 2010 issue of BioSupply Trends Quarterly *at www.BSTQuarterly.com.*

"The final mile of vaccine distribution is always getting it to the patient," says Chris Ground, senior vice president national accounts, FFF Enterprises Inc. "One of the things they didn't do this time was to engage the normal seasonal vaccine distribution channels. Mass distribution of flu vaccine is handled very efficiently every year, but because H1N1 went through public health channels, there was a degree of micromanagement that resulted in tons of vaccine being left sitting in warehouses and never reaching patients at all."

Interestingly, given the timeline of events, vaccine manufacturers actually did a phenomenal job getting the vaccine to market as quickly as they did. The media backlash that resulted from the delay was ironic, since initial outcries claimed the vaccine was not available soon enough. Later, resistance arose when the idea that the vaccine was produced too quickly (and was therefore unsafe) began to surface, fueled by vaccine opponents on the Internet. "One of the lessons we learned is that we had a new level of communication we may not have been used to: social networking," says Mark B. Johnson, president, American College Preventive Medicine.[5] "People were spreading messages quickly online — including rumors that the vaccine was unsafe — and many people trusted some of these sources more than they trusted the government. There was a lot of mistrust regarding official messages."

True to its unpredictable nature, the H1N1 flu virus did not grow as well as expected in eggs, apparently requiring different conditions to thrive than its seasonal counterpart.

Overpromising on vaccine delivery became a major public relations problem for both the government and public health agencies — especially when the guidelines for who would be immunized changed. Initially envisioned as a mass vaccination of the general public, the limited vaccine supplies demanded that only those in high-risk groups, such as pregnant women, receive priority access to early batches. In many cases, harried physicians and pharmacists were left holding the bag, having

to explain unexpected shortages to a frustrated public. "You had vaccine trickling out to providers who would then advertise that they had [the 2009] H1N1 vaccine, and you'd have a riot on your hands with too many people showing up to get vaccinated," says Ground. "When you classify high-risk groups, you have to be very careful how you communicate. If you reach out to providers who handle high-risk groups and let them act as the filter to get the word out about vaccine availability, you can hopefully avoid a lot of the problems we saw last fall."

Packaging Problems and Foreign Suppliers

A clear lesson learned during the development of the 2009 H1N1 vaccine was that problems can occur at many points during development. Between the testing, packaging, allocation and distribution, plenty can go awry. For H1N1, unexpected packaging issues arose as officials described a "logjam" at factories attempting to get the completed vaccine into vials.

Another problem highlighted by the 2009 H1N1 pandemic is that America is extremely dependent on European manufacturers for its flu vaccine. The Health and Human Services Department has contracted with five different companies to make influenza immunizations for the U.S. market: Novartis, Sanofi Pasteur, CSL, AstraZeneca unit MedImmune and GlaxoSmithKline. While Sanofi has a flu vaccine plant in Pennsylvania, until recently, remaining flu vaccines for the U.S. market have been made in other countries. Many experts caution that in the event of a serious pandemic, countries would likely prioritize vaccine supplies for their own citizens. Indeed, as the U.S. awaited the arrival of its 2009 H1N1 vaccine last year, Australia's CSL sent notification that shipments would arrive later than promised because it was providing batches to Australians first (Australia's winter occurs during our summer months, and their flu season was already in full swing).

U.S. health officials have been actively looking into streamlining vaccine manufacturing methods, while decreasing our dependence on imported vaccines. In November of last year, Novartis opened its first U.S. flu vaccine plant, and it will be the first in the country slated to make flu vaccines out of cells instead of eggs.[6] In a statement, Novartis said, "If licensed in an emergency, the facility will be ready to respond to a pandemic as early as 2011. The plant is planned to be running at full-scale commercial production in 2013."

A Fire Drill for Future Pandemics

In many ways, the vaccine challenges that arose during the 2009 H1N1 outbreak served as a fire drill that is hoped will improve our capacity to respond to future pandemics. During a March 2010 webinar titled "Lessons Learned from H1N1," William Schaffner, MD, FACPM, professor and chairman, Department of Preventive Medicine, noted that despite some unexpected glitches, response to the pandemic was very good at the federal, state and local levels. He also commented that in the absence of widespread vaccination clinics, the American public became quite adept at various nonmedical means of fighting the flu.

Interestingly, given the timeline of events, vaccine manufacturers actually did a phenomenal job getting the vaccine ready as quickly as they did.

"The fundamental way to prevent influenza is to vaccinate as many people as possible," Shaffner said. "We learned that when you don't have a vaccine, there are still things you can do to prevent illness — sneezing in your elbow, washing your hands and practicing social distancing can all help. If we didn't vaccinate as many people as we intended, we certainly did teach America how to sneeze." ❖

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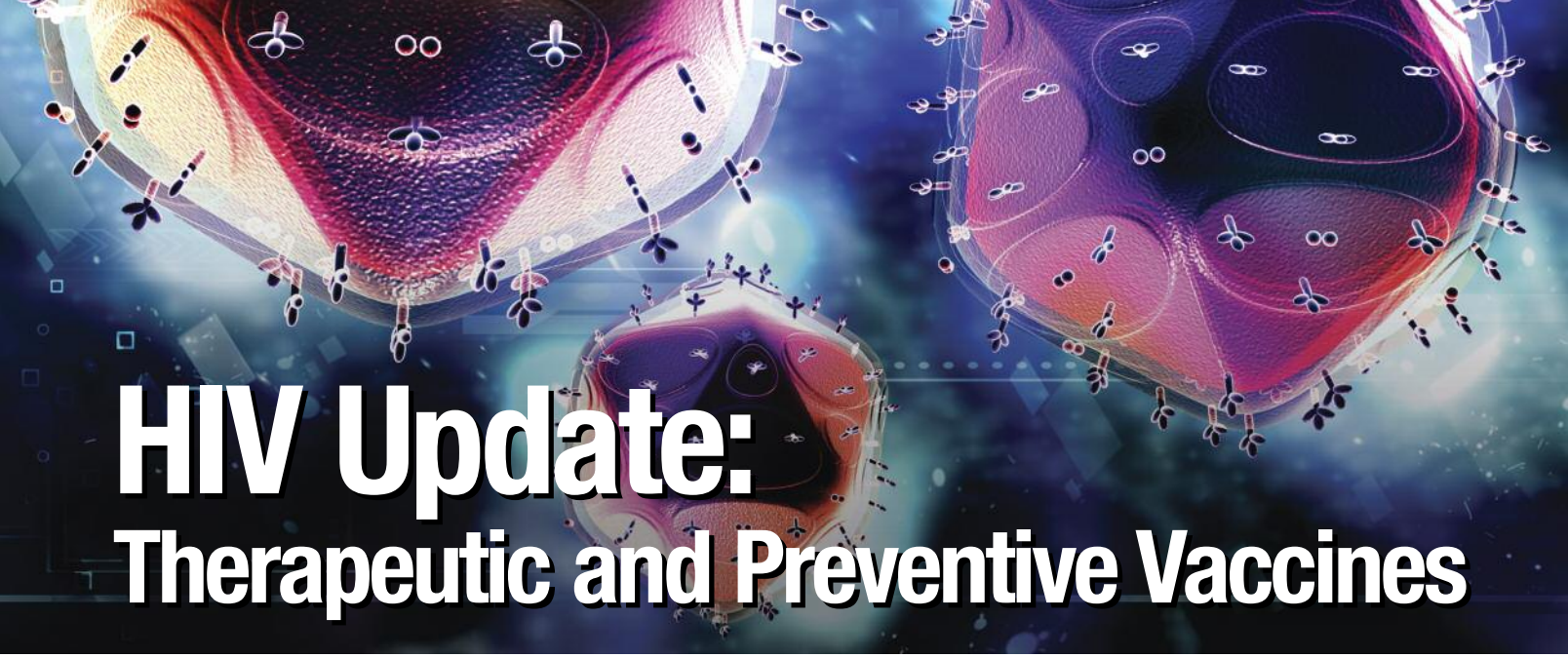

HIV Update: Therapeutic and Preventive Vaccines

The search for a preventive and therapeutic vaccine for HIV has long been studied. A look at past and current research shows just how far we've come.

By Amy Scanlin, MS

It is estimated that there are more than one million people in the U.S. living with HIV and 33 million people worldwide.[1] This number is expected to grow, in part because it is inevitable that some with HIV will transmit the disease to others, but also because treatments for those infected are improving and prolonging lives.

While growth in the number of new HIV infections likely will increase, some statistics show promising news that in recent years, that rate of increase is stabilizing. Newly transmitted infections have decreased dramatically since the 1980s when, at its peak, 92 out of every 100 persons with HIV transmitted the disease. But, by the year 2006, that rate dropped to approximately 5 percent, with 53,000 cases newly diagnosed. Today, it is estimated that 56,300 are diagnosed yearly.[2,3] Education efforts are largely responsible for this decline, with research showing that the majority who know they are infected with HIV will take steps to prevent transmitting the disease to others. There also have been dramatic decreases in the incidence of transmission between mother and child with anti-AIDS drugs.

However, other sources, such as the newly released World Health Organization worldwide study, show a troubling picture of AIDS as the leading pathogenic cause of death for women ages 15 to 44 years. Obviously, the impact and the burden of this statistic vary by world region.[4]

Prior to the introduction of antiretroviral medications, opportunistic infections (those that are more severe and frequent due to a suppressed immune system) were the leading cause of mortality and morbidity in HIV-infected individuals in the U.S. Today, these infections continue to be a significant cause of death. The HIV virus mutates rapidly, there are numerous subtypes, and there appears to be a limited window for a vaccine's ability to stop or delay infection — perhaps within hours or days. But scientific prevention of the disease through new testing methods, as well as efforts to produce a vaccine for both prevention and as therapy, offer hope. Researchers are focusing on both the cellular and humoral response of the immune system, and as with many other vaccines, looking not only at prevention but at halting disease progression.[5]

Vaccine Research

The National Institute of Allergy and Infectious Diseases (NIAID) has supported more than 100 vaccine trials involving more than 60 different products. Dozens of those HIV vaccine candidates entered Phase I clinical trials in the last 15 years. And, while many of these produced a positive HIV immune response, few have proceeded to Phase IIa and Phase IIb trials.

STEP study. One of the better known studies in HIV vaccine research is the STEP Study, which tested an Adeno 5 (adenovirus type 5) vaccine candidate in 3,000 volunteers in the U.S., Latin America and Australia.[6] However, the study was eventually stopped, explains Dr. Alan Fix, branch chief of Vaccine Clinical Research of the NIAID's Vaccine and Prevention Research Program, "because a planned DSMB [data safety monitoring board] review of the data indicated that the vaccine neither prevented infection nor resulted in lower viral load among those who became infected." He adds that results at the time also indicated more infections among those vaccine recipients who were Ad5 seropositive and uncircumcised compared to placebo recipients with those attributes.

Although the trial was stopped, scientists are still gleaning

data from the study, such as mapping epitopes to determine their importance in the immune response, and will be continuing the analysis for potentially years to come.

Current research. Initially, the search for a preventive treatment looked for vaccines to produce an antibody response. When that approach didn't appear to be successful, the focus turned to eliciting a cellular response. Fix explains that "the various types of vaccines previously and currently being explored include peptide, protein, DNA and viral and bacterial vectors." While HIV vaccines under study do produce antibodies that can cause a positive test for HIV, more sophisticated tests can distinguish the vaccine antibodies from the actual HIV virus.[7]

Recombinant vector vaccines use attenuated non-HIV viruses as vectors to deliver copies of HIV genes into the body's cells, allowing the body to use the instructions in the genes to produce HIV proteins, stimulating an anti-HIV response. According to the National Institutes of Health AIDS information fact sheet, "Some of the virus vectors being studied for HIV vaccines include ALVAC- (a canarypox virus), MVA- (a type of cowpox virus), VEE- (a virus that normally infects horses) and adenovirus-5- (a human virus that doesn't usually cause serious disease) based vectors."[3]

Research on the body's production of antibodies as prevention is still under way as scientists work to identify broadly neutralizing antibodies that could create a multiple attack on an HIV virus. Several of these antibodies have been identified so far, and it is thought that these greater numbers of antibodies could broadly neutralize the virus even though it mutates.[8]

In November of 2009, the NIAID announced a new direction in generating HIV antibodies by focusing on a specific, vulnerable location on the non-mutating HIV surface protein gp120. By binding the HIV neutralizing antibody, b12, to the specific initial attachment site on the gp120, the immune system can be taught to effectively make HIV antibodies, binding to the functional viral spike, and forming a normal trimeric structure.[9]

The search for an HIV/AIDS vaccine has been one of the longest and most well-funded in history.

Prime-Boost Vaccination

Researchers also are looking at the effectiveness of combining vaccine strategies. Called "prime-boost vaccination," this technique stimulates different immune responses that may further protect against HIV infection.

RV144 Phase III. The RV144 Phase III study conducted by the U.S. Army and the Thailand Ministry of Public Health was the first to show an investigational vaccine that demonstrated an ability to protect against HIV infections.[10] The RV144 Phase III HIV Vaccine Trial tested the ALVAC-HIV vaccine (prime), and AIDSVAX B/E vaccine (boost), the combination of which is based on common circulating HIV strains in Thailand.

More than 16,000 non-HIV infected volunteers participated in the study, half of whom received the prime boost and half of whom received a placebo. While all volunteers were HIV negative, all had an average risk of becoming infected. The study found that the prime boost combination group had a 31.2 percent lower rate of HIV infection compared with the placebo group, although the vaccine did not affect the amount of virus in the blood of those who became infected.[11] "The results were promising and scientists are working to understand their significance," says Fix. "Scientists are determining the best use of the collected specimens in trying to identify a correlate for protection."

HVTN 505 Phase II. Another Phase II NIAID study presently under way is the HVTN 505 that uses four immunizations of two investigational vaccines developed by NIAID scientists. The primer vaccine is a DNA-based recombinant and is given three times during an eight-week period, followed by one vaccination of a weakened Ad5-based recombinant vaccine that will help to stimulate the immune system.

The study participants are more than 1,300 circumcised HIV-free men between the ages of 18 and 45 years who have no circulating antibodies to the Ad5 virus. The study group, though not infected at the time the study began, is at a higher risk of infection. Researchers will look at what happens to viral load of those who become infected during the study and whether there is a lower rate of infection and a slower progression of the disease, as well as the safety of the two protocols.[12]

MTN 003 Phase II. A prevention tool currently being tested is a topical microbicide antiretroviral drug, tenofovir, in the form of a gel or cream applied to the vagina and oral tablets of tenofovir or a combination of tenofovir and emtricitabine known by the brand name Truvada. Both methods are used once daily.

Known as the VOICE (Vaginal and Oral Interventions to Control the Epidemic) study, the study of 5,000 uninfected women ages 18 to 45 in Africa began in September 2009 and

will last approximately three and a half years. Scientists will be looking at which regimen, pill or gel, is followed more consistently, the frequency that study participants become infected, as well as the safety of the two measures.[13] A companion study will look at the effects on bone mineral density, since an ongoing study has shown that tenofovir can have an adverse effect on both the spine and hip, though this effect has not adversely affected health.[14]

HIV Treatment

There are 31 FDA-approved antiretroviral medications in five separate classes on the market.[15] These medications inhibit the HIV virus from fusing with cellular membranes (fusion/entry inhibitor); prevent the HIV RT enzyme from converting from HIV RNA into HIV DNA (reverse transcriptase [RT] inhibitors); prevent the HIV virus from producing infectious particles (protease inhibitor); or prevent the HIV virus from integrating into a target host cell (integrase inhibitor). To prevent the virus from developing a resistance to any one treatment, doctors like to use the fifth class of treatment, or a combination of two antiretroviral drugs, called highly active antiretroviral therapy (HAART). A medication that prevents the HIV virus from maturing also is being studied.

The Centers for Disease Control and Prevention's newly updated *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents* places a greater emphasis on effective antiretroviral therapy critical for preventing and managing infections.[16]

Scientific prevention of the disease through new testing methods, as well as efforts to produce a vaccine for both prevention and as therapy, offer hope.

Quality of Life of the Infected

A number of studies aimed at improving quality of life and reducing infections in those with HIV are under way. Positive results show that while we wait for an approved therapeutic vaccine, infected patients will have options that improve their overall health and make HIV a manageable chronic condition.

Reducing tuberculosis (TB) in HIV positive patients with a booster vaccine. Lung infections are the biggest cause of death among those infected with HIV. A study conducted at Dartmouth Medical School found that a booster TB vaccination of Mycobacterium vaccae can prolong the life of those who also had previously received the Bacillus Calmette-Guérin (BCG) vaccine earlier in life. In the Phase III study of 2,000 participants in Tanzania over the course of seven years, the incidence of TB was reduced by 39 percent.

Improvements in visceral fat with tesamorelin. A serious side effect of HIV treatments can be abnormal fat distribution and abnormal lipid and glucose metabolism.[17] It appears from recent studies that tesamorelin, a growth hormone-releasing factor, can help patients improve their levels of visceral fat and waist circumference without having detrimental metabolic effects.

Two Phase III, randomized, placebo-controlled studies of more than 400 patients have shown the negative effects of increased blood lipids. The patients taking tesamorelin saw an 11 percent decrease in visceral fat and improvements in waist-to-hip ratio, compared to only a .6 percent decrease in the placebo group. At the end of a six-month follow-up, the patients taking tesamorelin had an average 17.5 percent loss of visceral fat versus a loss of only 1 percent in the control group.

Reducing viral load. Studies have shown that those who have a reduced HIV viral load take longer to become sick and develop AIDS. It is also thought that those who have a reduced viral load will have less chance of transmitting the virus to others. These are just two of the reasons some scientists see viral load reduction as a key to reducing AIDS in the next decades.

Researchers at the South African Center for Epidemiological Modeling and Analysis (SACEMA) are proposing a voluntary mass testing of the most at-risk individuals and placing those found to be infected on a lifelong AIDS treatment of antiretroviral drugs. Early testing and treatment would be the key to long-term success.[18]

One Step Forward, Two Steps Back

The search for an HIV/AIDS vaccine has been one of the longest and most well-funded in history. Yet, at times, it has seemed to be one step forward and two steps back. However, building on previous studies, scientists are getting closer than ever to learning how the virus works and how it can be prevented and stopped. The search for a preventive cure and therapeutic treatment continues with growing promise. ❖

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References available on request by emailing editor@IGLiving.com.

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

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

5.2 Reactions Reported to Occur With IGIV Treatment

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

Renal Dysfunction/Failure

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

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

Thrombotic Events

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

Aseptic Meningitis Syndrome (AMS)

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

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

Hemolysis

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

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

Transfusion-Related Acute Lung Injury (TRALI)

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

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

5.3 Transmissible Infectious Agents

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

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

5.4 Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

Table 2: (Continued)

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

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

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

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

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

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

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

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

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

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

7.2 Serological Testing

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Hizentra has not been evaluated in nursing mothers.

8.4 Pediatric Use

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

Hizentra was not evaluated in neonates or infants.

8.5 Geriatric Use

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

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US License No. 1766

Distributed by:
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Kankakee, IL 60901 USA
Based on March 2010 version

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Vivaglobin®
Immune Globulin Subcutaneous (Human)

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

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

CSL Behring

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

PRECAUTIONS

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

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

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

Vivaglobin® should not be mixed with other medicinal products.

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

*Excluding infections

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

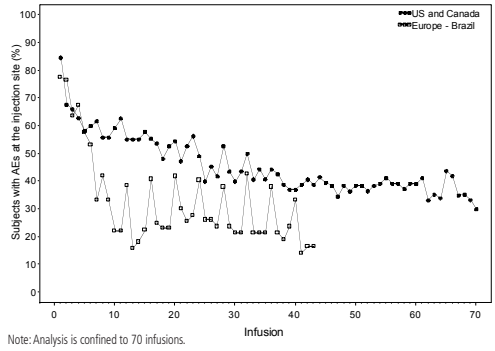
Related Adverse Event (≥ 2 AEs) (Number of Infusions: 3656)	**No. of AEs (Rate**)**
Adverse Events at the Injection Site	1787 (49%)
Non-Injection Site Reactions	
Headache	59 (1.6%)
Rash	9 (0.2%)
Nausea	9 (0.2%)
Nervousness	4 (0.1%)
Asthenia	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)
Skin disorder	3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

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

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

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

Figure 1: Subjects Reporting Local Site Reactions By Infusion



Note: Analysis is confined to 70 infusions.

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

HOW SUPPLIED

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

NDC 0053-7596-01	3 mL carton
NDC 0053-7596-03	Box of ten 3 mL vials
NDC 0053-7596-10	10 mL carton
NDC 0053-7596-15	Box of ten 10 mL vials
NDC 0053-7596-20	20 mL carton
NDC 0053-7596-25	Box of ten 20 mL vials

STORAGE

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

Based on April 2009 revision

Early Detection: A Potential Cure for Cancer

Scientists are working on a variety of molecular and imaging diagnostics to advance the early detection rate of cancer.

By Ronale Tucker Rhodes, MS

Each year, nearly 1.5 million Americans are diagnosed with cancer, and more than one-third of these cases result in death. Indeed, cancer is responsible for one in every four deaths in the country.[1] Those affected by cancer know that it is highly treatable, but only if detected early; just ask the more than 11 million cancer survivors and their families.[2]

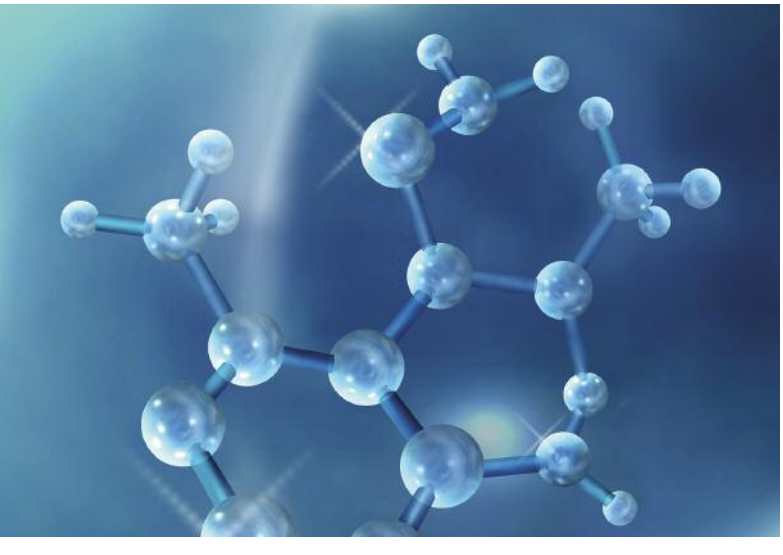
One of those survivors is North Carolina Rep. Bob Etheridge, who was diagnosed with melanoma. That experience led him to introduce a bill to promote early detection for cancer, which was passed by the U.S. House of Representatives in January. The bill designates May as Early Detection Month, and is designed to enhance public awareness of screening for all forms of cancer by encouraging activities to educate the public

about early detection and cancer screening.[1] "I am thankful that my melanoma was caught and treated," Etheridge says. "By passing legislation to designate public awareness of cancer screenings and early detection, we can make sure that all Americans have the chance I had to get treatment and survive. Early detection saves lives and focuses healthcare on prevention of diseases, rather than simply treating them after they have occurred."

Etheridge isn't alone in his quest. President Obama has pledged to conquer cancer "in our time," and his first proposed budget included $6 billion for cancer research by the National Institutes of Health. This proposal will build on the ongoing progress that is being made in detecting cancer early enough to save lives. For example, statistics show that the risk of death from cancer in American men is 20 percent lower than it was 20 years ago.[2] Yet, while this is an improvement, the risk of death still remains too high. To answer this problem, an impressive amount of research is aimed at early detection, as well as the development of new diagnostic tools. Currently, two promising areas offer hope: molecular diagnostics that can be detected with genetic biomarkers and imaging diagnostics — both of which employ non-invasive and minimally intrusive techniques.

Molecular Diagnostics

Simply defined, molecular diagnostics is the use of DNA, RNA and proteins to identify biomarkers that can be used to distinguish abnormal from normal status. Biomarkers may include genetic, epigenetic, proteomic and metabolomic markers, as well as those derived from imaging and general physical examination-based techniques. The two leading research areas contributing to the identification of biomarkers are genomics and proteomics.[3]



Genomics is the study of complex sets of genes, how they are expressed in cells (what their level of activity is) and the role they play in biology. In cancer research, genomics is the study of a small network of genes and how they work together to influence a tumor's biology and behavior.[4] For biomarker discovery using genomics, DNA samples for testing can be obtained least invasively from sputum samples, but alternatives include tissue biopsy, surgery samples and serum/plasma samples.[3]

The key to a potentially cancer-free future lies in the blood where proteins and other molecules hold critical information about cancer.

Unfortunately, genomic-based biomarkers are limited compared with protein biomarkers. This is because the mRNA and protein levels don't necessarily correspond, which means the genomic-based biomarker may not fully reflect the underlying characteristics of cancers. Protein biomarkers, on the other hand, can detect genetic alterations, such as chromosomal abnormalities, oncogenes and tumor-suppressor genes, which can play a role in early diagnosis and prediction of cancer progression.[3]

Identifying and analyzing protein patterns in the blood is a field of study called proteomics. The process involves extracting proteins in the blood, urine or other tissue to be analyzed by a technique known as mass spectrometry, which creates patterns of protein fragments. An artificial-intelligence computer program then sorts the unique protein signatures and identifies the discrepancies in protein patterns between people with and without cancer. Those proteins linked to cancer can then serve as biomarkers to detect early disease and predict responsiveness to therapy or the likelihood of recurrence. They also can be used to classify the genetic subtype of the cancer so that treatment can be better tailored to the individual.[5]

In the past 10 years, the rapid development of proteomic technologies has brought about a massive increase in the discovery of novel cancer biomarkers.[6] According to the Fred Hutchinson Cancer Research Center (FHCRC), the key to a potentially cancer-free future lies in the blood, where proteins and other molecules hold critical information about cancer. The FHCRC was selected by the National Cancer Institute (NCI) to lead one of two research teams dedicated to developing

simple blood tests to detect the earliest signs of cancer and other diseases, so they can be treated as early as possible, when cure rates are highest. The initial aim of the NCI-funded consortium is "to identify serum biomarkers — proteins in the blood that either alone or in combination are detected in altered amounts in people with cancer or who are at high risk of developing the disease."[5]

While the study of proteomics still has a long way to go for the detection of many cancers, FHCRC scientists have already developed a blood test to predict whether leukemia will return after treatment, and they have identified a protein that could lead to a new blood test for ovarian cancer. Most recently, scientists identified two proteins in the blood that could become important prognostic markers for long-term survival in breast cancer patients.[7]

The ultimate goal of biomarkers, says Leland H. Hartwell, president and director at the FHCRC, is risk assessment that can lead to prevention and early detection leading to cures.

The FHCRC isn't the only organization making headway in biomarker discovery using proteomics. The following are some interesting proteomics developments:

• Scientists have found that cancer patients produce antibodies that target abnormal glycoproteins (proteins with sugar molecules attached) made by their tumors. This suggests that antitumor antibodies in the blood may provide a fruitful source of sensitive biomarkers for cancer detection. The study, supported in part by the National Cancer Institute (NCI), part of the National Institutes of Health, appears in the Feb. 15, 2010, issue of the journal *Cancer Research*.[8]

• United Kingdom scientists have designed a method to detect prostate cancer using surface-enhanced resonance Raman scattering (SERRS). The researchers combined the technique with a biological method called an enzyme-linked immunosorbent assay (ELISA) to detect a prostate-specific antigen in which elevated levels in serum indicate the cancer's presence. The process involved first analyzing antigen levels in human serum samples using ELISA, and then using gold nanoparticles with SERRS to measure antigen concentration. This resulted in detection of picograms per milliliter antigen levels, lower than the current limit of nanograms per milliliter in cancer screening. In the future, they hope to be able to use SERRS to detect multiple proteins that indicate the presence of disease.[9]

• Quanterix, a company created by Tufts University chemistry professor David Walt, is developing a way to detect trace quantities of proteins in the blood that could be an early warning sign for cancer or a neurodegenerative disease like Alzheimer's or Parkinson's. The company's new CEO, Dave Okrongly, says its test is about 1,000 times more sensitive than the gold-standard ELISA because proteins in the bloodstream generally come in trace amounts too small to be detected by the standard ELISA tests. The Quanterix system, on the other hand, is designed to detect thousands of single molecules simultaneously with proprietary chemistry and what the company calls "a relatively simple" instrument with a light source, optics, a digital camera and an automated handling system.[10]

Outside the field of proteomics, some other interesting research is being conducted to identify biomarkers. A new technique known as dielectrophoresis (DEP) uses an electrical field to separate particles according to their differing electrical properties. American scientists are using this technique to separate live and dead leukemia cells to provide an automated system for early cancer detection. Yet, because conventional DEP requires direct contact between the electrodes and sample fluid, leading to problems such as contamination and bubble formation, these scientists have developed a new approach known as contactless-DEP in which the electrodes are separated from the sample by a thin barrier to avoid any problems. The scientists are now optimizing the device, which they say could allow selective separation of cells from biological fluids for cancer diagnosis and differentiation of cells at different stages of the disease.[11]

Other studies conducted by ChromoCure and the Mayo Clinic have validated the theory of aneuploidy, a chromosomal theory of cancer. Aneuploidy is an abnormal number of chromosomes, and is a type of chromosome abnormality. An extra or missing chromosome is a common cause of genetic disorders (birth defects), and some cancer cells also have abnormal numbers of chromosomes. For some time, controversy has existed over whether aneuploidy is a cause or a consequence of cancer, and these studies point to the former. The study appeared in the Jan. 15, 2010, edition of *Cancer Research*.[12]

While these are just a tiny sampling of the number of molecular diagnostic studies currently in development, they show great promise. The ultimate goal of biomarkers, says Leland H. Hartwell, president and director at the FHCRC, is

risk assessment that can lead to prevention and early detection leading to cures, and he uses an interesting metaphor when he likens disease prevention and early detection to"the continuous data acquisition occurring in commercial aircraft." He explains: "With 40,000 flights a day in the U.S., it is very rare for a commercial plane to crash, and when it does, it is more often due to human error than mechanical failure. This is because 10,000 sensors are accumulating and reporting information, continuously providing early warning of a pending failure." Hartwell asks, then, "Could we monitor our bodies with the same sophistication?" Science is showing that, in fact, it can. And, while it is a major piece of the puzzle for detecting and preventing cancer, it is not the whole picture.[13]

Imaging Diagnostics

Many have criticized the search for biomarkers for cancer because they believe biomarkers won't be specific enough or they can lead to overdiagnosis or overtreatment. But, Hartwell says that those critics fail to appreciate other developments that can accompany better blood tests. "Finding cancer proteins in the blood will probably never be sufficient for a cancer diagnosis," he says, "but it is sufficiently informative to warrant more expensive imaging tests that localize the abnormality."[13]

Imaging technologies are currently available to screen for all kinds of potential illness, including cancer. The more publicized tools, of course, are full-body screening. These include electron beam tomography (EBT), CT scans employing a computer helical CAT scan (also known as spiral scanning), positron emission tomography (PET) scans and magnetic resonance imaging (MRI). The smallest cancers can now be detected through these scans, long before they might be visible on standard chest X-rays or other tests.

EBT. When undergoing EBT, patients lie fully clothed on a table while an electronic beam traverses the body area and produces three-dimensional images for examination by a technician or physician. These detailed graphics can be viewed from every possible angle, and images can be stored, filmed or transmitted. The major medical application for which this design technology was invented in the 1980s was for imaging the beating human heart, and other structures, such as arteries, that move several times their diameter during each heartbeat. An advantage of EBT scans is that they can be swept with far greater speed, which is important to prevent blurring of moving structures during the scan.[14]

Spiral CT. In spiral CT scans, the X-ray tube rotates around the reclining patient as the examination table moves forward through the scanner. The rotating tube, thus, provides a spiral view of the body. Spiral CT scanning can permit greater visualization of blood vessels and internal tissues, such as those within the chest cavity.

Both EBT and spiral CT scans are rapid and non-intrusive for the patient, exposure to radiation is minimal, and results are provided within minutes.[14]

PET. A PET scan observes processes in the brain, heart and other internal organs, and its importance for early cancer detection is its ability to trace metabolic changes in cancer cells that are different from other tissues. In cancer cells, there are increased rates of blood flow, amino acid flow, DNA synthesis and glucose transport compared to normal tissues, and a PET scan can detect these changes within a high range of efficiency.[15] In recent years, some facilities have combined PET scans with CT scans into one procedure, which provides a more complete picture of a tumor's location and growth or spread than either test alone. Researchers hope that PET/CT scanning will improve healthcare professionals' ability to diagnose cancer, determine how far it has spread and follow patients' responses to treatment.[16]

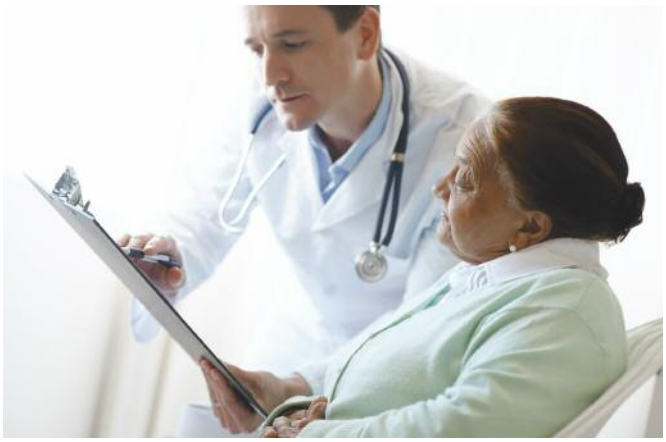
MRI. An MRI uses two safe and natural forces, a magnetic field and radio waves, to produce vivid images of internal body parts, including soft tissues, muscles, nerves and bones.[17] Much like CT scans, an MRI can produce three-dimensional images of sections of the body, but an MRI is sometimes more sensitive

than CT scans for distinguishing soft tissues.[18] MRIs are commonly used to screen for breast cancer. In women with a high inherited risk of breast cancer, screening trials of MRI breast scans have shown that MRI is more sensitive than mammography for finding breast tumors.[19]

Other minimally invasive imaging technologies also are emerging. One of these is the WavSTAT Optical Biopsy System developed by SpectraScience, which is indicated for use as an adjunct to lower gastrointestinal (GI) endoscopy. The WavSTAT uses a spectrophotometry technique known as laser induced fluorescence (LIF) that shines a color laser light onto and excites tissues to emit a returning fluorescent signal, which indicates whether tissue is normal, precancerous or cancerous. Those tissues are then immediately analyzed by a software algorithm, allowing physicians to determine whether a biopsy should be taken.[20] This type of minimally invasive procedure goes one step further than non-invasive imaging technologies because, since the scope is already in place, a biopsy can immediately be taken.

The Future of Early Detection

"It is estimated that the pharmaceutical industry spends about $20 billion a year developing cancer therapeutics, most of which have marginal benefit," says Hartwell. What's surprising, though, is that "the investment in diagnostic approaches is minuscule in comparison with their potential impact on improving patient outcomes" — due not just to few technology advances or too little time. Instead, says Hartwell,



there are other reasons, equally formidable. The Institute of Medicine has published a monograph on cancer biomarkers that identifies several challenges beyond the stage of discovering biomarkers. "First, reimbursement for new diagnostics is poor, a situation that discourages the commercial investment that is needed. [And,] current models for obtaining FDA approval for new diagnostics are nearly as difficult and costly as for the approval of drugs."[13]

Despite these challenges, many scientists are forging ahead to discover further molecular diagnostics, as well as develop new imaging tools. Their efforts promise to bring about even greater success for early detection of all cancers, and could lead to the eventual eradication of cancer itself. ❖

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

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Myths and Facts: Pneumonia

With millions of people dying annually worldwide from pneumonia, the facts about who is at risk of contracting this disease and how it can be prevented have never been more important.

By Jim Trageser

Pneumonia is the single deadliest infection in the world.[1] In the United States, pneumonia is the No. 1 cause of death from infection. Half of all pneumonia cases are adults over the age of 65, and often they are hospitalized.[2] And, children and those immunocompromised are just as susceptible to contracting pneumonia.

Yet, pneumonia also is one of the oldest diagnoses available to physicians. Hippocrates described the symptoms more than 2,300 years ago, and even then he said it was the disease "named by the ancients."[3] In 1875, Edwin Klebs first identified bacteria in the airways of patients who had died of pneumonia. By 1884, researchers following up on Klebs' work had shown that pneumonia could be caused by more than one type of bacteria.[4]

But while we've known since the earliest days of civilization (and perhaps before) that the lungs are prone to infection —

and that those infections can quickly become life-threatening — it wasn't until relatively recently that we understood what can cause this disease. And it's even more recent that we've had the capability to prevent many potential cases of pneumonia through vaccination.

Despite these advances, many myths persist about pneumonia, and patients often don't know when to contact a doctor because symptoms of pneumonia often mimic those of a chest cold or the flu. And, those most at risk — the elderly, infants and people with compromised immune systems or other underlying health issues — are not always educated about the seriousness of pneumonia, or the ways in which they can help to prevent it. To help bridge this gap, getting out the truth about pneumonia is the best way to counter the many myths that stand in the way of effective treatment.

Separating Myth from Fact

Myth: Pneumonia is rare; only people who are HIV positive or have lung cancer get pneumonia.

Fact: Pneumonia kills more than four million people a year. Even in the United States, 1.2 million people were hospitalized in 2006, and more than 55,000 died from it.[1] While many of these patients did have underlying health issues, others were perfectly healthy before contracting pneumonia.

Myth: Pneumonia is caused by the pneumococcus bacteria.

Fact: While pneumococcus-caused pneumonia is the most common cause of pneumonia in the United States, pneumonia also can be caused by viruses, fungi, parasites and chemical agents, as well as non-pneumococcus bacteria.[5] However, the bacterial pneumonia — including pneumococcus-caused cases — generally are more severe than viral cases, particularly among children and the elderly.[6]

Myth: It is easy to diagnose pneumonia.

Fact: Symptoms of pneumonia often are similar to those of a chest cold or bronchitis. According to the National Institutes of Health, symptoms of pneumonia include high fever, chills, cough with phlegm, shortness of breath, chest pain when coughing or breathing, nausea, vomiting or diarrhea and feeling worse after having the flu or a cold.[7]

Infants and newborns may not exhibit any symptoms, or they may show lethargy, restlessness or fatigue. The elderly may display milder symptoms, even a lower temperature, and also may exhibit sudden changes in mental alertness.[7]

By listening to a patient's breathing through a stethoscope, looking at X-rays of the lungs or having a culture taken from the patient's sputum, a case of pneumonia can generally be differentiated from a common cold or the flu.

Myth: Pneumonia will go away on its own.

Fact: Most cases of pneumonia caused by bacterial infections will clear up with bed rest at home within a few weeks. And, cases caused by viral infections perhaps may last a little longer. However, the elderly, infants and those with compromised immune systems or other underlying health challenges need to seek immediate medical care to prevent the infection from worsening.

Myth: Only the elderly and those patients with compromised immune systems are at risk of serious complications from pneumonia.

Fact: Pneumonia is the leading cause of death in children,[8] and even otherwise healthy people can and do contract pneumonia.

Myth: Viral pneumonia is more dangerous because it can't be treated with antibiotics.

Fact: Most cases of viral pneumonia (generally caused by an influenza virus) are mild. However, while viral pneumonia will generally abate on its own within a month or so, patients are at increased risk of also contracting a bacterial infection in their lungs while sick with viral pneumonia.[5]

Some cases of viral pneumonia can be treated with antiviral medications if caught within the first 48 hours of infection. Drugs such as rimantadine or amantadine may be used to treat pneumonia caused by influenza A, while oseltamivir and zanamivir are used to treat both influenza A and B.[9]

Myth: Hospitalized patients don't have to worry about catching pneumonia.

Fact: The medical profession actually classifies pneumonia by where it is contracted (as well as the underlying pathogen causing the infection or inflammation), and hospital-acquired

pneumonia is one of those classes. The risks associated with hospital-acquired pneumonia are exacerbated since those contracting it are usually already ill. Patients on a ventilator may be especially prone to pneumonia. There also is the risk of being exposed to resistant bacteria in a hospital, which makes treatment more difficult.[10]

While the CDC recommends that all adults 65 and older receive the pneumococcal polysaccaride vaccine, it also calls for all children under 5 years of age to receive the pneumococcal conjugate vaccine.

Myth: There is no way to prevent pneumonia.

Fact: While the pneumococcus vaccine isn't widely known among the public, it has been available since 2000 and is highly effective at preventing pneumonia from the pneumococcus bacteria (Streptococcus pneumoniae). Even those patients who have received the pneumococcus vaccine and later contract pneumonia have, on the whole, milder cases of pneumonia and fewer serious complications.[11]

Because the seasonal flu virus also can cause pneumonia, an annual flu vaccine is a good preventive measure. In addition, since the Haemophilus influenzae type b (Hib) bacterium is responsible for pneumonia (as well as meningitis), the Hib vaccine, usually part of the course of infant vaccines in the United States, also is part of a good defense.[12]

The Centers for Disease Control and Prevention (CDC) points out that general rules of good hygiene always apply. Frequently washing hands with hot water and soap, keeping hard surfaces like door knobs and countertops sanitized, and coughing and sneezing into a tissue or even a sleeve all can help to slow the spread of bacteria and viruses that cause pneumonia.

Myth: A pneumonia vaccine is good for only one year.

Fact: Only one dose of pneumococcal polysaccaride vaccine is needed. However, it is recommended that individuals age 65 and older who received their first dose when they were younger than 65, and it has been more than five years since then, get a second dose.[13]

Myth: Only the elderly need to get the pneumococcus vaccine.

Fact: While the CDC recommends that all adults 65 and older receive the pneumococcal polysaccaride vaccine, it also calls for all children under 5 years of age to receive the pneumococcal conjugate vaccine.[14] The pneumococcal polysaccaride vaccine also is recommended for children 24 months and older if they have high risk factors (HIV, sickle cell or other immunological disease) for pneumococcal disease. In addition, many states require the pneumococcal conjugate vaccine for any child in a daycare environment.[15]

Dispelling the Myths Now

Pneumonia is one of the oldest known diseases, so it seems only logical that individuals would be knowledgeable about its causes and how to prevent it. On the contrary, pneumonia is still a leading killer, giving evidence to the fact that this knowledge isn't readily available. Countering the growing number of myths surrounding the disease with the real facts can help to change that. And, with flu season not far off, now is never a better time. ❖

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Humate-P is the only von Willebrand factor (VWF) concentrate that:

- Is approved for the treatment of spontaneous and trauma-induced bleeding in all types of von Willebrand disease (VWD)
- Can be used for prevention of excessive bleeding during and after surgery for all procedures
- Contains high molecular weight multimers of VWF—important for correcting the coagulation defect in patients with VWD[1]

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Close as it gets to normal VWF

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

Important Safety Information

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

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

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

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

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

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

1 INDICATIONS AND USAGE

1.1 Hemophilia A

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

1.2 Von Willebrand Disease (VWD)

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

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

IU = International Units.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Events (VWD Patients)

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

5.2 Monitoring for Intravascular Hemolysis

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

5.3 Monitoring VWF:RCo and FVIII Levels

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

5.4 Transmission of Infectious Agents

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

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

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

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

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Studies Experience

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

Treatment of Bleeding Episodes in VWD

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

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

Prevention of Excessive Bleeding During and After Surgery in VWD

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

Table 5: Hemorrhagic Adverse Events in 63 Surgical Subjects

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

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

7 DRUG INTERACTIONS

None reported.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Hemophilia A

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

VWD

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

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

8.5 Geriatric Use

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

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Inherited Disorder

Living with a rare bleeding disorder her whole life, Jennifer Wakefield has found meaning and purpose helping others — especially children — cope with chronic illness.

by TRUDIE MITSCHANG

IT STARTED WITH a nosebleed. Jennifer Wakefield was no more than 1 year old at the time, and while even a small bleed for a child that young would be frightening, for Jennifer and her parents, the situation proved terrifying and unstoppable. After losing an alarming amount of blood, Jennifer was rushed to the hospital where she eventually was diagnosed with type III von Willebrand disease.

Von Willebrand disease, an inherited disorder that affects the blood's ability to clot properly, is named for Dr. Erik von Willebrand, who first described the condition in 1926. Von Willebrand disease is the most common inherited bleeding disorder, affecting as much as 1 percent of the population. Unlike hemophilia, which affects mostly boys, von Willebrand affects boys and girls equally. Type III, Jennifer's disease state, is by far the most severe.

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A Childhood Interrupted

When Jennifer was diagnosed with von Willebrand in 1968, treatment options were few. Even diagnostic accuracy was limited, and testing of family members to determine how Jennifer contracted the disease proved inconclusive (it was later determined that the disorder stemmed from her father's side of the family). Jennifer's treatments initially involved time-consuming plasma infusions to replace her missing von Willebrand factor and factor VIII.

"When I was a child, I pretty much spent two weeks out of every month at the hospital," the Clinton, Mich., resident recalls. "There were even teachers and study areas in the children's wing for kids like me who spent so much of their time there."

By the time Jennifer was 10, treatment protocols evolved, and she became one of the first homecare infusion patients in her area. Later, as an adolescent, Jennifer struggled with one of the issues unique to females with bleeding disorders: excessive bleeding during menstrual cycles. After a particularly heavy cycle left her hospitalized, Jennifer took her physician's advice and opted for a hysterectomy at age 19. She's never looked back.

Jennifer was diagnosed at 1 year old with type III von Willebrand, and now also has HIV and hepatitis C, byproducts of the tainted hemophilia blood supply in the 1980s.

"It changed my life," Jennifer says. "After the hysterectomy, I was really healthy and I had such a sense of relief — it really was one less thing to worry about."

A Second Diagnosis Brings Setbacks

As a young adult, Jennifer lived a reasonably normal life for many years, moving to California, attending college, embarking upon a career and getting married. Unfortunately, her reprieve from a life defined by chronic illness

A Closer Look at von Willebrand Disease

There are three types of von Willebrand disease:

- Type I is the most common and the mildest form of the disease. It is characterized by a decreased level of von Willebrand factor in the blood.
- Type II is characterized by an abnormality in the blood's von Willebrand factor.
- Severe, or type III, von Willebrand is characterized by nearly nonexistent levels of von Willebrand factor and factor VIII (the protein that helps with blood clotting).

Signs and Symptoms

The symptoms of von Willebrand disease vary depending upon the type and severity of the disorder, but many patients exhibit the following:

- frequent, large bruises from minor bumps or injuries
- frequent or hard-to-stop nosebleeds
- extended bleeding from the gums after a dental procedure
- heavy or extended menstrual bleeding in women
- blood in stools from bleeding in the intestines or stomach
- blood in urine from bleeding in the kidneys or bladder
- heavy bleeding after a cut or other accident
- heavy bleeding after surgery

ended in 1991, when at her doctor's insistence, she was tested for HIV.

"Because of the contaminated blood products that circulated back in the 1980s, most patients with bleeding disorders were encouraged to get tested for HIV back then," Jennifer says. "I had no symptoms and did not want the test, so naturally I was devastated when I learned I was HIV positive."

A newlywed with what she thought was her whole life ahead of her, Jennifer remembers spiraling into depression following her HIV diagnosis, widely considered a death sentence in the early 1990s. Eventually, her passion for life and fighting spirit helped her overcome this physical and emotional setback. "One day, I woke up and realized that I still felt good, I had a wonderful supportive husband, and despite the diagnoses, I needed to get on with my life," Jennifer explains.

One of the many challenges inherent in dealing with multiple chronic illnesses is the onslaught of medication side effects. Some of Jennifer's HIV medications, for example, have caused von Willebrand-related joint bleeding around her knees (she's had four knee surgeries and a total knee placement). "It was difficult finding HIV medications my body could tolerate," Jennifer says. "When you have a bleeding disorder, certain medications for HIV can actually cause bleeding. It's a real Catch-22."

In addition to von Willebrand and HIV, Jennifer also was diagnosed with hepatitis C in 1993, another byproduct of the once-tainted blood supply used for hemophilia treatment. Still, Jennifer

One of the many challenges inherent in dealing with multiple chronic illnesses is the onslaught of medication side effects.

considers herself fortunate to have had access to some of the country's best medical care, including several renowned physicians at the Henry Ford Hospital in Detroit. Today, she is free from hepatitis, and her HIV is under control, but the ongoing and long-term impact of von Willebrand disease is something she deals with daily. Physical therapy helps her debilitating shoulder and knee problems, and a strong support system of family and friends keeps her from falling prey to self-pity.

Living to Give

Never content to sit on the sidelines, Jennifer is active in support groups and volunteers as an advocate for those with bleeding disorders. A board member for the Hemophilia Foundation of Michigan, she is actively planning the organization's annual "SpringFest," Michigan's largest consumer education conference for people with blood disorders, including children and their parents. The event typically attracts more than 500 attendees from across the state.

"My 10-year-old niece has type I von Willebrand, and I'm taking her to SpringFest so she can meet other kids like her," Jennifer says. "When I was a kid, there was so little information and virtually no support. Now, there are kids' camps, workshops and support groups. It's wonderful to be a part of something that can improve the quality of life for the next generation of patients living with this disease." ❖

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

Diagnostic Testing

A combination of blood tests may be required to diagnose von Willebrand:

- von Willebrand factor antigen to measure the amount of von Willebrand factor in the blood
- von Willebrand factor ristocetin (ris-to-SEE-tin) cofactor activity to test the functioning of the patient's von Willebrand factor
- factor VIII clotting activity
- von Willebrand factor multimers, if one or more of the first three tests are abnormal. It shows the structure of the patient's von Willebrand factor to determine the type of von Willebrand the patient has.

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:

Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

U.S. License No. 1646

Distributed by:

Octapharma USA Inc.
121 River Street, 12th floor
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

Leading by Example

"Leaders don't resist innovation, they symbolize it."

— David Ogilvy

By Trudie Mitschang

AS A FORMER public health physician, Dr. Vas Narasimhan has a personal passion for eradicating vaccine-preventable diseases. His notable accomplishments are many, from working with the Botswana Minister of Health to launch the first campaign to treat HIV/AIDS in Africa, to his most recent high-profile role working with the federal government and public health agencies to bring the A(H1N1) 2009 influenza vaccine to market in time to help fight last year's pandemic. In his leadership role as Head, Vaccines North America for Novartis, Narasimhan is someone who makes it a point to lead by example.

True leadership skills often surface under pressure, and 2009 presented Novartis Vaccines with a daunting challenge: how to appropriately respond to a deadly influenza outbreak, and quickly develop and deliver a vaccine that would help protect a panicked public. The company, with Narasimhan at the helm of its North American operations, rose to the occasion, delivering 90 million doses of bulk influenza vaccine to the U.S. government by early 2010, a scant few months from the time the virus was first identified.

"As the largest supplier of pandemic vaccine to the U.S. government, we had to manage a very rapid scale-up in a short amount of time," Narasimhan says. "Naturally, manufacturers faced a lot of scrutiny from various government stakeholders who had concerns about their ability to deliver the vaccine in time. It was challenging, but I believe it was, in the end, a success."

Many criticisms have arisen in the wake of the A(H1N1) 2009 pandemic, with accusations of missteps and miscalculations hurled in numerous directions. Still, if there is a lesson to be learned, Narasimhan says it is always better to be over-prepared when dealing with an unpredictable virus.

"I don't believe it's realistic to think you can develop a plan that will fit every possible pandemic scenario, because we simply don't know what these viruses will do or how they will behave," he explains. "There will be those who say it was overblown or that we developed too much vaccine, but I'd prefer this scenario to one in which we under prepared and things turned more deadly than anticipated."

The measure of a good leader is often best analyzed by a team's track record and growth.

A New Vaccine Addresses a Deadly Disease

Earlier this year, the Novartis Vaccines division accomplished a significant goal when it received U.S. Food and Drug Administration approval of Menveo, a vaccine to prevent meningococcal disease, the leading cause of bacterial meningitis, for use in people 11 to 55 years of age. The approval represents an important milestone for adolescent immunizations in the U.S. According to the Centers for Disease Control and Prevention, approximately 16 million adolescents between the ages of 11 and 18 are at risk and remain unprotected against meningococcal disease, a troubling statistic since the disease is characterized by its ability to rapidly kill or debilitate previously healthy adolescents.

"Novartis has a long history and tradition of leading through innovation and vaccine technology, and our goal is to continue driving research and innovation to bring needed vaccines to market. Menveo is the culmination of 10 years of dedicated effort and the first manifestation of that goal for our meningococcal disease franchise in the United States," notes Narasimhan. "We plan to expand the indication to children, eventually to include infants, which is part of our longer-term goal to eradicate this killer disease completely."

Because of his background in public health, Narasimhan believes educating the marketplace on vaccine benefits is

essential when it comes to reaching out to all sectors, including advocacy groups, patients and physicians. As part of its disease education and Menveo marketing efforts, for example, the company has engaged meningococcal survivors to share their experiences with various stakeholders.

"Physicians want to hear from survivors (or people who have suffered from the disease) because it reminds them from a clinical and public health standpoint why meningococcal disease is so dangerous and why Menveo, as a vaccine indicated to prevent the disease, is so important," he says. "With preventive disease, you are dealing with healthy people and you often can't see what impact you are having. However, the impact becomes clear when the disease is no longer prevalent or is eradicated, like in the case of polio. These forums put a face on the disease."

Innovation and Technology Pave the Way

Narasimhan says that as the industry looks at the future of vaccine technology, the emphasis will be on less common diseases, particularly those impacting populations beyond the borders of the United States and Europe. Novartis Vaccines seems well-equipped to meet these changing demands — it was recently recognized for having the industry's best research and development pipeline at the 2010 World Vaccines Congress.

"We are working very hard at developing new technologies and vaccines for pediatric illnesses and new patient groups such as hospitalized patients, the immune-compromised and the elderly," Narasimhan explains. "We want to open up areas where new vaccines can be used to prevent disease. We're also focused on expanding our geographic presence in regions like Asia and Latin America to better meet the needs of populations that have not historically been addressed by the vaccine industry."

"Vaccines are the most transformative public health development of the past hundred years."

The measure of a good leader is often best analyzed by a team's track record and growth. When Narasimhan joined Novartis Vaccines' U.S. operations, the division consisted of a small group of people. Today, the group has grown to more than 300 strong, and is characterized by a culture and work environment that fosters an entrepreneurial spirit. Narasimhan says he empowers team members by encouraging them to take ownership of ideas and initiatives. By all accounts, he leads with a compelling vision and sense of purpose that influences every aspect of the business.

"Empowerment means driving adaptive change within the organization so that over time, individuals learn to seize opportunities without waiting for someone to give them direction," he says. "You need to keep oversight of course, but the only way to succeed is for everyone to feel they can take ownership and be leaders in their day-to-day work."

Narasimhan adds that the culture at Novartis Vaccines thrives on a deep commitment to public health and intervention. Like Narasimhan, his team members feel a sense of urgency when it comes to meeting the global demand for life-saving vaccines.

"The vaccine industry is very fortunate to be at the intersection of business and public health," he says. "Vaccines are the most transformative public health development of the past hundred years — there's so much that can be done to address public health problems around the world, and the only way to solve these problems is to break down walls between the industry, the government and non-governmental stakeholders. I want to be a part of that solution." ❖

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

For technical questions regarding any Novartis Vaccines product, please contact our Medical Information department at **800-244-7668, or visit www.novartisvaccines.com.**

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> Awarded the largest US government contract to supply H1N1 vaccine

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NOVARTIS
VACCINES

Chronic IG Therapy Options: They Just Keep Getting Better

By KEITH BERMAN, MPH, MBA

TRADE-OFFS. They've always been there for people who are prescribed immunoglobulin (IG) therapy, particularly those with primary immunodeficiency disorders (PIDD) who require chronic dosing to keep serious infections at bay. Only a few decades ago, PIDD patients faced the unhappy trade-off between frequent, very painful deep intramuscular injections of 16% immune serum globulin or the prospect of being overcome by a potentially life-threatening bacterial infection such as pneumonia. When the first intravenous immunoglobulin (IVIG) products arrived in the 1980s, requiring less frequent and far more comfortable injections, the misery of intramuscular injections became a thing of the past.

But as generally safe and effective as it is, IVIG therapy isn't without risks or limitations. Many patients can recurrently experience a spectrum of mild or moderate adverse reactions such as fatigue, headache, fever, chills, dizziness, nausea and vomiting. And, a far more serious IVIG-related issue concerns the small share of patients whose health problems dictate that overall administered fluid volume be minimized to the extent possible. This includes patients with renal dysfunction or impaired cardiac function resulting from a prior myocardial infarction or congestive heart failure.[1]

IVIG Volume Heads Down

One way to reduce the infused volume is to administer divided doses on different days. But a better and far more convenient solution is to simply concentrate the product. Three manufacturers — Baxter Healthcare, CSL Behring and Talecris Biotherapeutics — have done just that by reformulating their original 5% IVIG products to a 10% concentration, effectively cutting the infused volume by half. Two others — Grifols and Octapharma — expect their new 10% formulations to be approved shortly.

IG manufacturers are addressing product drawbacks head on with product innovation.

Another benefit of a more concentrated IVIG product is less time needed to infuse it, which can translate into cost savings from reduced nursing and infusion room time.

Suddenly, Under the Skin Is In

Over the years, physicians infusing IVIG preparations have learned how to reduce the frequency and extent of non-serious adverse events by slowing the rate of infusion and by premedicating with drugs such as acetaminophen, antihistamines or corticosteroids.[2] But for patients with persistent tolerability problems, physicians discovered long ago that protective levels of IG could be administered subcutaneously with fewer systemic side effects. So few, in fact, that the first subcutaneous immunoglobulin

When thrombotic risk is high in hereditary antithrombin deficiency

Proceed Safely

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

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

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

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

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

Important Safety Information

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

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

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

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

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

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

Talecris BIOTHERAPEUTICS

Thrombate III® antithrombin III (human)

Printed in USA November 2009 TH86-1109

THROMBATE III®
Antithrombin III (Human)

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

FOR INTRAVENOUS USE ONLY

DESCRIPTION

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

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

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

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

INDICATIONS AND USAGE

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

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

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

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

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

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

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

PRECAUTIONS

General

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

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

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

Laboratory Tests

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

Drug Interactions

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

Pregnancy Category B

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

Pediatric Use

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

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

ADVERSE REACTIONS

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

CAUTION

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U.S. federal law prohibits dispensing without prescription.

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08939599-BS

(SCIG) introduced in 2006 — CSL Behring's 16% Vivaglobin product — can be self-administered at home. But, again, there are trade-offs.

While IVIG is usually infused only once every three to four weeks in PIDD patients, SCIG must be administered at least weekly due to the fact that only a very limited volume can be injected under the skin during a single session. These subcutaneous volume restrictions also necessitate two or more needle sticks at a session, as well as patient training on the use of a syringe pump, specialized tubing and proper methods to safely deliver the product. Itching or burning at the injection site is common, but can be either prevented or effectively treated with antihistamines.

Not surprisingly, four years after the launch of Vivaglobin, roughly three-fourths of PIDD patients remain on the simpler and much less frequent IVIG therapy option.

Innovation May Yield Better Product Options

Like so many times before, immunoglobulin manufacturers are addressing these drawbacks head on with product innovation. CSL Behring has recently introduced a 25 percent more concentrated SCIG preparation called Hizentra. Talecris Biotherapeutics is expected to introduce its own product in the near future. But, arguably, Baxter is now working on the biggest potential leap for patients now on SCIG or considering SCIG therapy. Acquired from Halozyme Therapeutics in 2007, Baxter's novel "Enhanze Technology" is designed to allow the patient to self-administer a lot more SCIG in a single session — enough, in fact, to permit the same frequency of administration as IVIG.

As generally safe and effective as it is, IVIG therapy isn't without risks or limitations.

Enhanze is a recombinant version of the naturally occurring human enzyme hyaluronidase, which breaks down a space-filling gel-like substance called hyaluronic acid (HA), which is found in tissues throughout our body. The job of this man-made hyaluronidase injected under the skin prior to SCIG infusion is to temporarily digest HA, thereby enhancing penetration and diffusion of much more SCIG than would otherwise be possible.

In a Phase I/II trial, 10 PIDD patients received monthly subcutaneous infusions with Enhanze HA followed by Gammagard Liquid 10% IVIG in doses ranging from 25.5 to 61.2 grams (255 to 612 mL) in a single site. Patients were infused at rates between 120 to 300 mL per hour, similar to IVIG administration rates. A Phase III trial in 80 adults and children with PIDD is now nearing completion. FDA approval will hinge on demonstrating safety and tolerability; if successful, we could see this exciting new product within the next two years.

Meanwhile, manufacturers also continue to strive for improvements to their IVIG offerings. Octapharma, for example, recently announced the first of a series of pivotal studies to evaluate a novel 10% "high purity" IVIG preparation. "Pre-clinical studies and initial clinical experiences have confirmed that a favorable tolerability profile may be expected," according to the study's coordinating investigator. A Phase III trial in PIDD patients is now under way.

Weighing IG Therapy Choices

Today and in the future, PIDD patients and their physicians will continue to weigh differences in time, convenience, treatment setting and adverse event profiles that apply for SCIG and IVIG to try to decide which product is best for them. As they improve and the trade-offs between these two product options diminish, that choice could become more difficult. I think we can all agree that would be a very pleasant new challenge to face. ❖

References

1. Sorensen, R. Expert opinion regarding clinical and other outcome considerations in the formulary review of immune globulins. *Journal of Managed Care Pharmacy*, 2007 Apr;13(3):278-83.
2. Skoda-Smith, S, Torgerson, TR and Ochs, HD. Subcutaneous immunoglobulin replacement therapy in the treatment of patients with primary immunodeficiency disease. *Therapeutics and Clinical Risk Management*, 2010;6:1-10.

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.*

BioProducts

POC Immunoassay Technology

The QL Care Analyzer (QLCA) provides printed medical lab quality results in less than 15 minutes, making it capable of delivering test results in the emergency room, doctor's office or emergency response vehicle. It employs chemical light generation or chemiluminescence (CL), the same technology used in medical labs, and uses a patented automated electronic process to trigger CL, which enhances light collection, speeds up marker binding and increases sensitivity. The pre-loaded disposable test cartridge is the size of a portable CD player, features an intuitive user interface touch screen and is capable of storing patient data for up to 5,000 individuals.
CardioGenics, (905) 673-8501, www.cardiogenics.com/ql_care_analyzer.html

Pulse IVR/IWR System for Clinical Trials

Pulse is a fully configurable platform that allows users to design and deploy clinical trial integrated response technology (IRT) systems, saving substantially on the development time of clinical trials. The Pulse platform contains pre-validated programs so developers do not have to spend time reconfiguring studies. It also gives more control to clinical program managers by allowing them to perform mid-study changes on the fly. For some studies, the platform will deliver a validated study program in just four weeks.
Endpoint Clinical, (888) 344-7899, www.endpointclinical.com

SES Update for CNS Clinical Trials

An upgrade to the hardware for the Signal Enhancement System (SES), a central nervous system clinical trial tool, allows patient interviews to be recorded and viewed in a more precise, higher-quality format. Designed to further improve clinical trials, the hardware features a newer, faster laptop with a 180-degree, higher-pixel motion-detecting camera and a high-quality USB microphone that can clearly record conversation up to 50 feet away. SES ensures that interviews are consistently conducted according to protocol and facilitates expert and consensus ratings.
The Cognition Group, (949) 369-1300, www.cognitiongroup.com

Prostate Cancer Test

The VIDAS fPSA rt Assay is a lab test, used along with digital rectal examination, to help diagnose prostate cancer in men age 50 years and older. The test measures how much free prostate-specific antigen (fPSA) is in a man's blood, relative to total PSA (tPSA). The test works by drawing a sample of blood from the patient that is then added to chemicals in the Free PSA test. When a specific chemical is added, a light reaction is produced and is measured inside an instrument. The amount of light emitted shows the level of fPSA in the blood. Then, the fPSA level is used with tPSA measured in the same sample to calculate the fraction of tPSA that is fPSA. The Free PSA test can be used only with the Total PSA test from the same company and on the same instrument system.
Biomerieux Inc., (800) 682-2666, www.biomerieux-usa.com

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IVIG Cuts Pain Intensity in Complex Regional Pain Syndrome

Patients with long-standing complex regional pain syndrome (CRPS) experienced significantly reduced average pain intensity after a single infusion of intravenous immunoglobulin (IVIG), according to a report by researchers at the University College London Hospitals Pain Management Center. Twelve patients suffering with CRPS for six to 30 months were randomly assigned to receive 0.5 grams/kg of IVIG or an equal volume of normal saline. After a washout period of at least 28 days, each patient was then crossed over to the alternative treatment.

Asked to rate their pain intensity on a zero-to-10 point rating scale, patients rated their pain experience 1.55 units lower during the six to 19 days following IVIG therapy than after saline injection (95% CI, 1.29 to 1.82; $P < 0.001$). In three of the 12 patients, reported pain intensity following IVIG administration was less than after saline by 50 percent or more. No serious adverse reactions to IVIG were reported.

While acknowledging that recruitment bias and chance variation could have influenced results in this small trial, the investigators noted that the observed response rate to IVIG in this crossover trial is consistent with results from a 2005 study evaluating IVIG in 130 patients with 12 chronic pain syndromes.

Goebel, A, Baranowski, A, Maurer, K, et al. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Annals of Internal Medicine*, 2010 Feb 2;152(3):152-8.*

Fibrin Sealant Well Tolerated, Easy to Use in Hernia Repairs

As an alternative to tissue-penetrating devices, Baxter Healthcare's Tisseel fibrin sealant product was evaluated in a 1,201-subject multicenter observational study throughout France to assess its safety and efficacy for atraumatic mesh fixation in inguinal hernia repair. This highly concentrated preparation of human fibrinogen and thrombin components was used in 526 procedures performed by "open" surgical techniques and 675 using laparoscopic repairs. The objective was to learn if use of this mesh fixation alternative to such tissue-penetrating devices as staples and sutures is associated with reduced postoperative bleeding, pain and other complications.

Local complications occurred in 4.7 percent of patients, including 3.0 percent with hematoma, 1.4 percent with seroma and a 0.3 percent recurrence rate. Patients reported, on average, minimal pain immediately after surgery and at one-month follow-up. Consistent with other studies assessing fibrin sealant, these results suggest that fibrin sealant may yield fewer of these complications than mechanical means of mesh fixation. The study authors concluded that Tisseel appears to be a well-tolerated, easy-to-use alternative to traditional, tissue-penetrating devices for mesh fixation in hernia repair. The results of large randomized trials now in progress are keenly anticipated.

Descottes, B, and Bagot d'Arc, M. Fibrin sealant in inguinal hernioplasty: an observational multicentre study in 1,201 patients. Hernia*, 2009 Oct;13(5):505-10.*

Alpha-1 Antitrypsin and Doxycycline Suppress Arthritic Changes in Mouse Model

University of Florida scientists were able to reduce development and progression of rheumatoid arthritis in an experimental mouse model by injecting an adeno-associated virus vector that expresses human alpha-1 antitrypsin (hAAT) together with a diet containing the drug doxycycline. Control group mice received doxycycline alone or saline. Animals that received combined hAAT gene therapy and doxycycline (a tetracycline-like antibiotic) had reduced macroscopic and histopathological changes in the joints in relation to the control groups.

Additionally, the hAAT/doxycycline combination inhibited interleukin-6 expression in lipopolysaccharide-stimulated NIH/3T3 mouse fibroblast cells, suggesting a contributing mechanism of arthritis inhibition. The investigators concluded that "a combination therapy using AAT and doxycycline holds promising potential as a new therapy for rheumatoid arthritis."

Grimstein, C, Choi, YK, Satoh, M, et al. Combination of alpha-1 antitrypsin and doxycycline suppresses collagen-induced arthritis. The Journal of Gene Medicine*, 2009 Oct 28 [Epub ahead of print].*

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	$60.302	$61.462
FLEBOGAMMA 5% DIF	Grifols	J1572	$71.982	$73.366
GAMMAGARD LIQUID	Baxter BioScience	J1569	$75.467	$76.918
GAMMAGARD S/D	Baxter BioScience	J1566	$60.302	$61.462
GAMUNEX	Talecris Biotherapeutics	J1561	$73.924	$75.346
OCTAGAM	Octapharma	J1568	$73.587	$75.002
PRIVIGEN	CSL Behring	J1459	$70.176	$70.176

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

Rates are effective July 1, 2010 through September 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%)	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
FLUZONE Pediatric	0.25 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90655
AFLURIA	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
FLUZONE	0.5 mL single-dose vial		
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

gamunex®

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

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, safely and effectively. See full prescribing information for GAMUNEX.

GAMUNEX (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified) 10% Liquid Preparation

Initial U.S. Approval: 2003

WARNING: ACUTE RENAL DYSFUNCTION and FAILURE

See full prescribing information for complete boxed warning.

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

INDICATIONS AND USAGE

GAMUNEX is an immune globulin intravenous (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

- **PI** – Most common drug related adverse reactions during clinical trials were headache and cough.
- **ITP** – Most common drug related adverse reactions during clinical trials were headache, vomiting, fever, and nausea.
- **CIDP** – Most common drug related adverse reactions during clinical trials were headache and fever.

To report SUSPECTED ADVERSE REACTIONS, contact Talecris Biotherapeutics, Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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Revised: October 2008

The PROOF is everywhere you look

GAMUNEX is the IGIV therapy supported by robust clinical trials

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

Important Safety Information for GAMUNEX

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

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

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

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

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

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

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

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

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

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

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

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