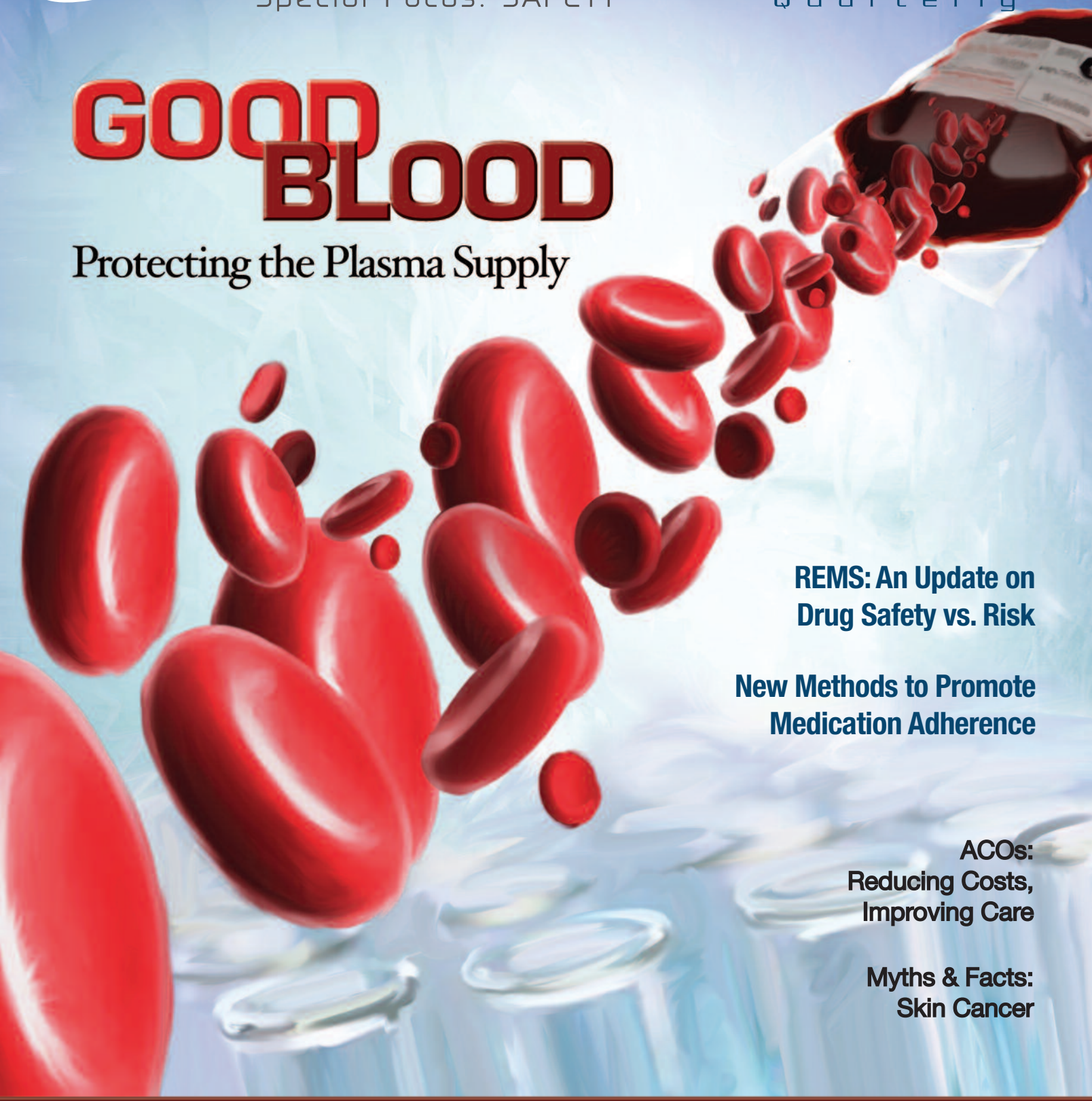
April 2011

BioSupply Trends

Special Focus: SAFETY

Quarterly



GOOD BLOOD

Protecting the Plasma Supply

REMS: An Update on Drug Safety vs. Risk

New Methods to Promote Medication Adherence

ACOs: Reducing Costs, Improving Care

Myths & Facts: Skin Cancer

The Fraud Behind Synthetic Colloids Research — Page 56

Developed Specifically for the Treatment of von Willebrand Disease

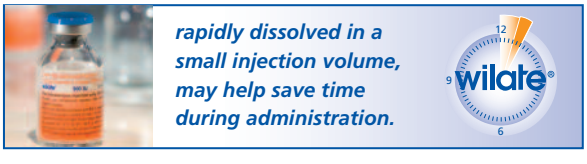
wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

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

Two convenient vial sizes

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



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

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

For More Information, Please Contact Us

Octapharma USA, Inc.
121 River Street
Suite 1201
Hoboken, NJ 07030
201-604-1130
www.octapharma.com

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

Medical Affairs:
usmedicalaffairs@octapharma.com
888-429-4535

Reimbursement:
usreimbursement@octapharma.com
Tel: 800-554-4440
Fax: 800-554-6744

www.wilateusa.com

octapharma
For the safe and optimal use of human proteins

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

INDICATIONS AND USAGE

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

DOSAGE FORMS AND STRENGTHS

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- None known.

USE IN SPECIFIC POPULATIONS

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

DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution

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

Dosage in von Willebrand Disease

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

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

Dosing Schedule

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

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

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

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

Treatment guidelines apply to all VWD types

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

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

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

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

HOW SUPPLIED/STORAGE AND HANDLING

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

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

Shelf life

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

PATIENT COUNSELING INFORMATION

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

Manufactured by:

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

U.S. License No. 1646

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Octapharma USA Inc.
121 River Street, 12th floor
Hoboken, NJ 07030

octapharma

For the safe and optimal use of human proteins

BioSupply Trends Quarterly

April 2011

Features

Special Focus: Safety

About BioSupply Trends Quarterly
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Spotlight On Safety

IN OUR LAST edition of *BioSupply Trends Quarterly*, I reflected on the obsession with safety that our plasma manufacturing partners consistently convey. As a specialty distributor of these same fragile proteins, our "safety first" approach and unwavering commitment to channel integrity could also be characterized as obsessive. Yet, when dealing with blood products, manufacturing and supply chain vulnerabilities are matched only by those of the patients who are in need of the life-saving and live-giving benefits that only a blood transfusion or blood plasma product can provide. As so eloquently expressed in our feature, Good Blood, the merging of someone else's life blood with your own is truly an act of faith, yet for those patients on the receiving end, there is rarely the luxury of choice. The real or perceived risks are generally trumped by the acute or chronic need.

You may recall the documentary that was released in the fall of 2010 titled *Bad Blood*, which recounted the circumstances that led to HIV contamination in the nation's blood supply. Our article Good Blood revisits this dark period of history for the industry with what we hope you will find to be an unbiased, accurate review of the many factors — from diminished blood supplies and understaffed health agencies to the ignorance and fear that surrounded HIV and AIDS — that combined to create the perfect viral storm. True to the old adage that every cloud has a silver lining, the AIDS epidemic served as a catalyst for industry improvement and reform. That today, according to the U.S. Centers for Disease Control and Prevention, the U.S. blood supply is considered the safest in the world is an achievement born of a "liberal dose of literal blood, sweat and tears."

Risk versus benefit is not an uncommon dilemma with regards to safety. Our article titled Risk Evaluation and Mitigation Strategies (REMS) gives an update on the FDA's new strategy to ensure that the safety of certain drugs outweighs their risks, with a focus on the abuse of prescription medications. When evaluating the risk profile of a drug, the potential for abuse, misuse, overdose, addiction or teratogenicity (ability to cause birth defects) poses unique considerations requiring REMS.

Ultimately, we hope that those in positions of authority who influence our industry have patients' best interests at heart. So our Industry Insight column titled A Fake and a Fraud that exposes a prominent clinical expert in fluid resuscitation therapy whose self-interest eclipsed his integrity is disheartening at best. And, in keeping with our theme of safety, our Myths and Facts: Skin Cancer feature is meant to help people understand the risks of sun exposure and how they can best protect themselves from this often-deadly disease.

We are keeping a close watch on healthcare reform, with two in-depth articles: New Transparency Reporting Guidelines Affecting Physicians and ACOs: Reducing Costs While Improving Care.

We hope you find this issue of *BioSupply Trends Quarterly* relevant and helpful as we all endeavor to serve patients in need of these essential biopharmaceutical products. ❖

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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Ronale Tucker Rhodes, MS

Assistant Editor
Cheryl Brooks

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Jennifer Kester
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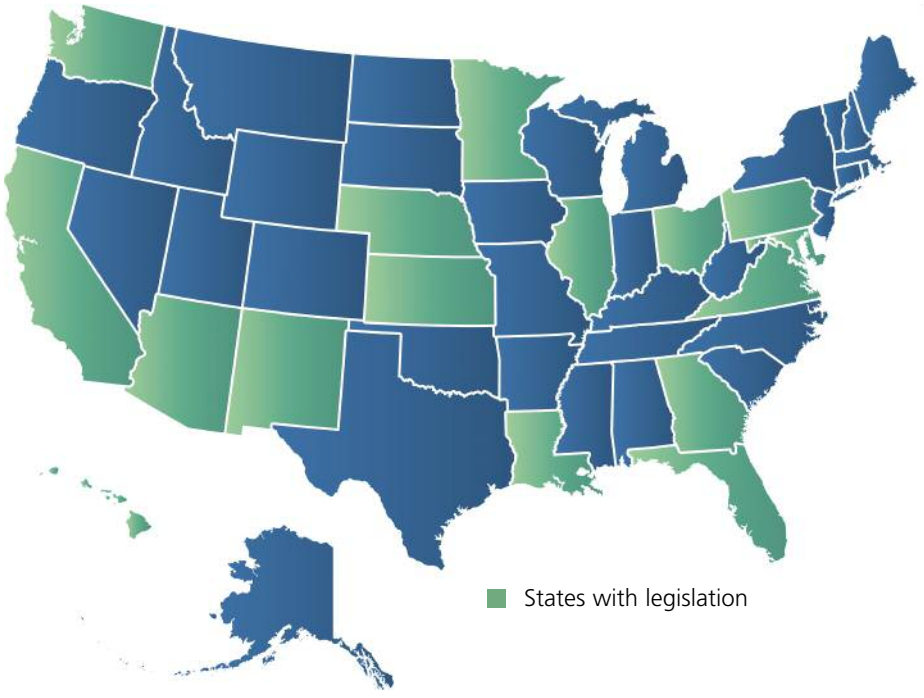
Please direct editorial, advertising and marketing communications to
41093 County Center Drive
Temecula, CA 92591
Ph: (800) 843-7477
Email: editor@BSTQuarterly.com

More Legislation Introduced to Ban Specialty Tiers in States



The introduction of legislation to ensure access by patients to high-cost therapies continues to increase throughout the country. As of this writing, 16 states have introduced legislation to eliminate the increased practice by private insurance companies to classify high-cost drugs under specialty tiers and/or coinsurance. These states include Arizona, California, Florida, Georgia, Hawaii, Illinois, Kansas, Louisiana, Maryland, Minnesota, Nebraska, New Mexico, Ohio, Pennsylvania, Virginia and Washington. Previously, the state of New York banned the classification of these drugs under specialty tiers or coinsurance because it found the practice discriminatory.

High-cost drugs included in specialty tiers and coinsurance are those that cost more than $600 and/or are infusible/injectable therapies that need to be provided through specialty pharmacies rather than retail pharmacies. This includes all intravenous immune globulin products, coagulation factor products, alpha-one products, as well as immune suppressants, interferons, immune modulators, anti-rejection medications for organ transplantation and chemotherapy drugs. There are no generic alternatives to any of these therapies. These drugs are used to treat genetic disorders and chronic and rare diseases, which include autoimmune diseases, cancer, cystic fibrosis, epilepsy, hemophilia, hepatitis, HIV/AIDS, lysosomal storage disease, multiple sclerosis, neuropathy, osteoporosis, primary immunodeficiency, and the list goes on.

States are using many approaches to deal with specialty tiers and coinsurance.

States are using many approaches to deal with specialty tiers and coinsurance. These therapies can be preventing plans from increasing coinsurance throughout a plan year, placing these therapies under catastrophic coverage so they are 100 percent covered once maximum out-of-pocket has been paid, and banning the practice of specialty tiers altogether, while capping out-of-pocket expenses on prescription medications.

Medicare Part D, the Federal Employees Health Benefits Program, Tricare and Employee Retirement Income Security Act (ERISA) plans remain subject to this practice, and, on average, these patients must pay 30 percent of the cost of the medication. The insurance companies argue that by not using specialty tiers, they would have to increase premiums and/or stop providing plans in the states that are trying to pass legislation similar to New York's. ❖

Hospital Outpatient Reimbursement Increased for 2011

The U.S. Department of Health and Human Services (HHS) has announced it will provide $750 million to fund new prevention and public health programs, made available through the new healthcare law's Prevention and Public Health Fund. This investment, an increase from the $500 million invested last year, will help prevent tobacco use, obesity, heart disease, stroke and cancer; increase immunizations; and empower individuals and communities with tools and resources for local prevention and health initiatives.

According to HHS, "The Prevention and Public Health Fund, part of the Affordable Care Act, is designed to expand and sustain the necessary capacity to prevent disease, detect it early, manage conditions before they become severe, and provide states and communities the resources they need to promote healthy living." For more information about this and last year's investments, go to http://www.hhs.gov/news/press/2011pres/02/20110209b.html. ❖

GOP Governors Demand More Exchange Flexibility

Twenty-one Republican governors signed a letter sent in February to U.S. Department of Health and Human Services (HHS) Secretary Kathleen Sebelius asking for more flexibility for states as they put together their own health exchanges. "Among the requested changes are granting states authority to choose benefits that meet the needs of their citizens; waiving provisions that discriminate against consumer-driven health plans, such as health savings accounts; and commissioning an independent assessment of how many people will be 'offloaded' into the exchanges by employers," according to the Republican Governors Association.

The letter states that if HHS does not agree to implement the recommendations, it should be prepared to operate the state-based exchanges "under its own auspices." The full text of the letter can be read at http://www.rga.org/homepage/gop-govs-ask-hhs-for-changes-to-healthcare-exchanges. ❖

Federal Government Proposes Healthcare Cuts

As of this writing, many cuts to healthcare spending are being proposed and expected. House Republicans expanded their list of cuts to government programs this year to $100 billion, and the House Appropriations Committee released its bill, which includes about $1.6 billion in cuts to the National Institutes of Health and $1.3 billion in cuts to the nation's community health centers. The bill also proposes cuts of about $923 million to the Centers for Disease Control and Prevention, $482 million to the Centers for Medicare and Medicaid Services, $386 million to health professions and $174 million to the National Health Service Corps. Simultaneously, some House Republicans are working on an amendment to the budget resolution that would defund healthcare reform. The current resolution funding the government was set to expire March 4. ❖

Medical Tort Reform Legislation Proposed

The House Judiciary Committee is working to pass medical tort reform legislation. Committee Chairman Lamar Smith, R-Texas, says the reform will include indexing the $250,000 cap on noneconomic damages to reflect inflation, providing greater specificity about how the legislation would treat intentional torts, and ensuring states' rights to set their own malpractice laws. It is likely this legislation will pass the House, but have a difficult time in the Senate. ❖

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

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

Some patients claim that they are being billed for their subcutaneous immune globulin (SCIG) for a date of service (DOS) other than the date their medication was filled, shipped or received. Is that an accepted practice?

SCIG is reimbursed under Medicare using the durable medical equipment, prosthetic, orthotics and supplies (DMEPOS) benefit. The DOS should be the date the prescription was filled. If the prescription was not filled via mail order, the DOS should be the day the medication was received by the beneficiary. Additionally, because Medicare may be a primary or secondary payer, providers servicing private pay patients are expected to follow Medicare standards when billing for SCIG.

Medicare claims review and adjudication procedures, section 4105.3, specifically states:

"Generally, for DMEPOS that is not mail order, the supplier's date of service (DOS) is the date of delivery to a beneficiary's home.… Generally, for mail order DMEPOS, the DOS on the claim is the shipping date. However, for mail order DMEPOS provided immediately subsequent to a hospital inpatient stay and/or DME immediately following a nursing home stay, the DOS is the later of the shipping date or the date of discharge."[1]

I have patients who have been using Gamunex subcutaneously off label for several years. Now that Gamunex-C has been FDA-approved for subcutaneous administration in primary immunodeficient patients, are there new codes to use for reimbursement?

Yes, there are new codes for Gamunex-C. Specifically, using Gamunex-C for subcutaneous administration requires the use of a HCPCS code modifier to distinguish the route of administration. Using the modifier code is especially important when billing Medicare.

The HCPCS code that is to be used for intravenous administration of Gamunex-C remains J1561. Billing for the subcutaneous route of administration of Gamunex-C requires the use of an additional modifier code. That HCPCS code is J1561-JB.

Keep in mind that if the patient has a preauthorization specifically for Gamunex, you may need to seek a new authorization request before you can bill using the new codes. Failure to do so could result in a denial of claim.

NDC numbers also are different for Gamunex-C:

Old NDC	New NDC
13533-0645-12 (1.0g, 10mL)	13533-0800-12 (1.0 g, 10mL)
13533-0645-15 (2.5g, 25mL)	13533-0800-15 (2.5g, 25mL)
13533-0645-20 (5.0g, 50mL)	13533-0800-20 (5.0g, 50mL)
13533-0645-71 (10.0g, 100mL)	13533-0800-71 (10.0g, 100mL)
13533-0645-24 (20.0g, 200mL)	13533-0800-24 (20.0g, 200mL)

For a comprehensive list of all codes needed to bill for Gamunex-C, go to http://www.gamunex-c.com/media/Gamunex-C_Coding_Guide_GX172-1110.pdf.

Is it true that Medicare will start denying claims for subcutaneous immune globulin (SCIG) as medically unnecessary if the provider bills for a pump that is not the least costly alternative (LCA)?

In June 2007, the Centers for Medicare and Medicaid Services (CMS) issued a statement that said the Freedom 60 infusion pump is the only allowable pump for the administration of SCIG therapy. Providers that choose to upgrade the pump to a more expensive option can do so and still attain partial payment that is no greater than the allowable amount for the Freedom 60 pump.

Then, on Dec. 16, 2010, CMS instructed CMS Durable Medical Equipment Medicare Administrative Contractors (DMEMAC) to no longer make partial payments for such claims as of Feb. 4, 2011, unless the item submitted for reimbursement is the LCA. Furthermore, if a provider bills for an item other than the LCA, the entire claim (including the drug) will be denied as medically unnecessary. This change will apply to all claims in which the DOS for the initial rental month is on or after Feb. 4, 2011. Subsequent claims with a determination LCA prior to that date will continue to be adjudicated using the LCA determination of that rental period.[2]

Are there other products with new reimbursement codes from CMS for 2011?

Yes, there are many new codes that were effective Jan. 1, 2011. Some of these include:

J0597: Injection, c-1 esterase inhibitor (human), berinert, 10 units, manufactured by CSL Behring.

J1559: Injection, immune globulin (Hizentra), 100 mg otherwise specified, 500 mg, subcutaneous immune globulin product manufactured by CSL Behring.

J1599: Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg. To be used for Gammaplex, manufactured by Bio Products Laboratory.

J7184: Injection, von Willebrand factor complex (human), wilate, per 100 IU VWF:RCo, manufactured by Octapharma.

Flu vaccine in multi-dose vials that previously were payable for Medicare with CPT code 90658 are now billed with Q codes:

Q2035: Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Afluria), manufactured by Merck.

Q2036: Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Flulaval), manufactured by GlaxoSmithKline.

Q2037: Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluvirin), manufactured by Novartis Vaccines.

Q2038 Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluzone), manufactured by Sanofi Pasteur.

Q2039: Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (not otherwise specified).

For a complete list of changes in HCPCS codes, go to https://www.cms.gov/HCPCSReleaseCodeSets/ANHCPCS/list.asp. ❖

What has changed regarding certification of homebound patients?

As of Jan. 1, 2011, the Centers for Medicare and Medicaid Services (CMS) mandated that as a condition of payment, a physician or non-physician practitioner (NPP) must have a face-to-face encounter with the patient. Documentation of that encounter must be presented on the certification of eligibility for patients with a start of care on or after Jan. 1, 2011. For more details about the new requirements, go to http://www.cms.gov/center/hha.asp.

Sources:

1. Department of Health and Human Services Healthcare Financing Administration. Medicare Carriers Claim Manual Part 3, Claims Process, Nov. 17, 2000. Accessed at https://www.cms.gov/transmittals/downloads/R1685B3.pdf .
2. DME website article template document number: TMP-EDO-0049 Release Date: 07/06/2010 Version: 1.0.

Ask Our Experts

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

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

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

FDA Approval

FDA Extends Shelf Life of Hizentra to 30 Months

The U.S. Food and Drug Administration has approved a supplemental Biologics License Application to extend the shelf life of Hizentra, Immune Globulin Subcutaneous (Human), 20% Liquid, from 24 months to 30 months. Stabilized with L-proline, a naturally occurring amino acid, Hizentra can be stored at room termperature (up to 25 degrees Centigrade or 77 degrees Fahrenheit) for up to 30 months, and because no refrigeration is necessary, it can be ready to use without warning, offering patients and physicians convenience and portability.

Hizentra is the first and only 20 percent subcutaneous immune globulin approved in the U.S. It is indicated for the treatment of primary humoral immunodeficiency, a group of disorders that result from a dysfunctional immune system that prevent patients from fighting off infections caused by common germs. ❖

Vaccines

Canada Approves New Flu Vaccine for Seniors

Health Canada has approved Fluad, a seasonal flu vaccine manufactured by Novartis for adults aged 65 years and older. Fluad is the first seasonal flu vaccine in Canada to contain an adjuvant (MF 59) to help boost the immune response to provide better protection against the flu. Studies have shown that Fluad enhances the vaccine's immune response in older adults, including those with chronic diseases, compared with conventional non-adjuvanted vaccines. Research also shows that Fluad can help protect against influenza strains not included in the vaccine. It has been licensed and used extensively in Europe since 1997, where more than 50 million doses have been administered. ❖

FDA Approval

FDA Approves First Drug to Treat Lupus

The U.S. Food and Drug Administration (FDA) has approved Benlysta (belimumab) to treat patients with active autoantibody positive lupus (systemic lupus erythematosus) who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives and non steroidal anti-inflammatory drugs. Benlysta is delivered directly into a vein (intravenous infusion) and is the first inhibitor designed to target the B-lymphocyte stimulator (BLys) protein, which may reduce the number of abnormal B cells thought to be a problem in lupus.

Two clinical studies involving 1,684 patients with lupus demonstrated the safety and effectiveness of Benlysta. The studies diagnosed patients with active lupus and randomized them to receive Benlysta plus standard therapy, or an inactive infused solution (placebo) plus standard therapy. Patients treated with Benlysta and standard therapies experienced less disease activity than those who received a placebo and standard-of-care medicines. However, African American patients and those of African heritage participating in the studies did not appear to respond to treatment with Benlysta.

Prior to Benlysta, the FDA last approved the drugs Plaquenil (hydroxychloroquine) and corticosteroids to treat lupus in 1995. Aspirin was approved to treat lupus in 1948. ❖

Research

Gene Therapy Successful in Treating Immune Disease

Several recent studies have proven gene therapy is successful in treating immune diseases. In a recent study, two young children with Wiskott-Aldrich syndrome (WAS) showed marked clinical improvements after receiving gene therapy. The study, performed by Jordan S. Orange, MD, PhD, an immunologist at The Children's Hospital of Philadelphia, in collaboration with European gene therapy researchers, reported that two 3-year-old boys diagnosed with WAS soon after birth were treated by first collecting some of their hematopoietic (blood cell-forming) stem cells, then transferring normal WAS genes into those cells and returning the cells to the boys' bloodstreams. After treatment, the patients experienced fewer and less severe infections, bleeding episodes decreased after platelet counts improved, severe autoimmune anemia disappeared in one boy, and severe eczema completely resolved in the other. Three years after the gene therapy, the clinical benefits persisted.

This study is the latest example of clinical success for gene therapy. In 2009, researchers from The Children's Hospital of Philadelphia and the University of Pennsylvania reported dramatic vision improvements in patients with Leber congenital amaurosis, a form of inherited blindness. In the same year, Parisian researchers announced success in treating adrenoleukodystrophy, the disease depicted in the movie "Lorenzo's Oil." And, scientists at the University of California are reporting preliminary clinical benefits of gene therapy for adenosine deaminase deficiency, an immune deficiency disorder related to "bubble boy disease." ❖

Research

Swine Flu Produces Protective Antibodies Against Other Flu Strains

A recent study has found that people infected with H1N1 swine flu produce antibodies that are protective against a variety of flu strains, which may help scientists eventually develop a universal vaccine.

Researchers at Emory University in Atlanta recruited nine people who had been infected with the pandemic H1N1 influenza virus, some of whom had been only mildly infected and some who had been severely infected and admitted to the hospital for treatment. Most had been treated with antiviral drugs. They then examined blood samples from both those patients and healthy controls and found that blood samples from the patients contained cells producing antibodies to the virus, while those from the healthy controls did not. Among the cells producing antibodies against pandemic H1N1, a considerable proportion produced antibodies that also could bind to a broad range of recent H1N1 influenza strains, as well as the Spanish H1N1 flu virus from 1918 and the bird H5N1 influenza strain. However, none of those antibodies could bind to the H3N2 influenza strain, which had been common in the previous year.

The researchers say this gives further support to the idea that vaccines that protect against a broader range of flu viruses may be possible. However, a universal flu vaccine is still a way off. ❖

Research

Prenatal Flu Vaccine May Prevent Flu in Infants

Prenatal use of the influenza vaccine may protect young infants against the flu, according to a new study in the February 2011 issue of *Archives of Pediatrics and Adolescent Medicine*. The study, which followed 1,269 women who delivered babies during one of three flu seasons and received information on maternal influenza vaccine and flu status in infants from 1,160 of them, showed that infants whose mothers received the influenza vaccine were 41 percent less likely to acquire laboratory-confirmed influenza virus infection and 39 percent less likely to be hospitalized for influenza-like illness. Infants younger than 6 months are not eligible for the influenza vaccine, putting them at higher risk of getting the flu, particularly those who are not breast-fed and who live in a risky environment. ❖

Research

New Test May Offer Better Cancer Screening

Scientists at Massachusetts General Hospital in Boston have developed a cancer test that is so sensitive it can spot a single cancer cell among a billion healthy cells, which may offer a better way to screen for the disease besides mammograms, colonoscopies and other less-than-ideal methods currently used. The test uses a microchip that resembles a lab slide covered in 78,000 tiny posts, like bristles on a hairbrush. The posts are coated with antibodies that bind to tumor cells. When blood is forced across the chip, cells ping off the posts like balls in a pinball machine. The cancer cells stick, and stains make them glow so researchers can count and capture them for study. "This is like a liquid biopsy" that avoids painful tissue sampling and may give a better way to monitor patients than periodic imaging scans, said Dr. Daniel Haber, chief of the hospital's cancer center and one of the test's inventors.

Currently, there is only one test on the market to find tumor cells in the blood: CellSearch made by Johnson & Johnson's Veridex unit. But, that test just gives a cell count; it doesn't capture whole cells that doctors can analyze to choose treatments. The new test's inventors are partnering with Johnson & Johnson to bring it to market. And, four cancer centers also will start studies using the test this year. Studies about the chip have been published in *Nature*, the *New England Journal of Medicine* and *Science Translational Medicine*. ❖

Research

New Inhaled Drug Protects Against Flu

Researchers in Japan have found that one inhaled dose of Daiichi Sankyo Co. Ltd.'s CS8958 (or laninamivir) worked better than Tamiflu to keep mice alive when infected with a normally deadly dose of H5N1 avian influenza. In the study, mice were given a single dose two hours after infecting them with H5N1, which experts fear could cause a pandemic, and also used it to prevent infection. The study was reported on in the Public Library of Science journal *PLoS Pathogens*, which covered dozens of ongoing studies of a new batch of influenza drugs being developed by a variety of companies. Daiichi Sankyo has applied for approval of the drug and aimed to bring it to market by March 2011. ❖

Drug Recall

Albuterol Inhalation Solution Voluntarily Recalled from Market

The Ritedose Corp. is voluntarily recalling its 0.083% Albuterol Sulfate Inhalation Solution, 3 mL in 25-, 30- and 60-unit dose vials. The product, which is a prescription inhalation solution administered via nebulization for the treatment and maintenance of acute asthma exacerbations and exercise-induced asthma in children and adults, is being recalled because the 2.5 mg/3 mL single-use vials are embossed with the wrong concentration of 0.5 mg/3 mL and, therefore, represent a potential significant health hazard.

The following lot numbers manufactured by The Ritedose Corp. under NDC: 0591-3797-83, 0591-3797-30 and 0591-3797-60 are included in the recall: 0N81, 0N82, 0N83, 0N84, 0NE7, 0NE8, 0NE9, 0NF0, 0P12, 0P13, 0P46, 0P47, 0PF0 and 0S15. Consumers should return the affected product to the place it was obtained. Wholesalers and retailers should return the product to: Total Product Destruction, Attn: Recall, 8025 Howard St., Spartanburg, SC 29303. For more information, call (803) 935-3995 or email recall@ritedose.com. ❖

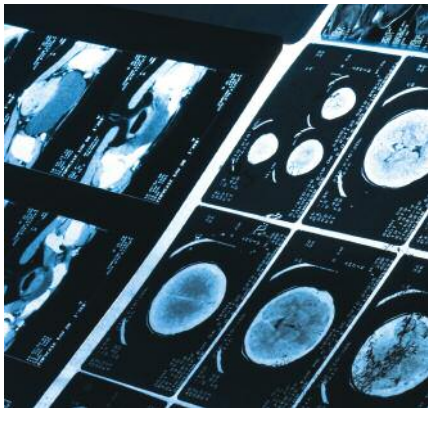
Research

Immune Modulation Therapy May Treat Ovarian Cancer

Researchers from the Royal Women's Hospital and Monash University in Melbourne, Australia, are testing immune modulation therapy to treat ovarian cancer. The therapy works on the theory that the immune system has a 10- to 14-day cycle during which it emits "inhibitor cells" that stop the body from fighting cancer. By giving small, tightly targeted chemotherapy doses at exactly the right time in the cycle, the inhibitor cells are blocked and the body's defense against the tumor is boosted. The chemotherapy comes in a pill that is taken every two weeks. Patients also must have a blood test every two days. To date, seven women with advanced, recurrent ovarian cancer have been given the therapy, and several have responded positively. ❖

Research

Autoimmune Skin Disease Is Associated with Neurologic Disease



Individuals with the autoimmune skin disease bullous pemphigoid appear more likely to have a diagnosis of neurologic disease, such as dementia and cerebrovascular disease, according to a study reported on in the November issue of *Archives of Dermatology*. Researchers at Oxford Radcliffe Hospitals, Oxford, England, assessed 90 consecutive patients with bullous pemphigoid and 141 controls without the condition. Among patients with bullous pemphigoid, 42 (46 percent) had at least one neurologic disease, compared with 16 controls (11 percent). Four major neurologic diseases were observed: cerebrovascular disease, dementia, Parkinson's disease and epilepsy. However, only rates of cerebrovascular disease and dementia were significantly greater among patients than among controls. And, of the patients with accurate information about the timing of their diagnoses, bullous pemphigoid was diagnosed after neurologic disease in most (72 percent), with a median time of 5.5 years between diagnoses. ❖

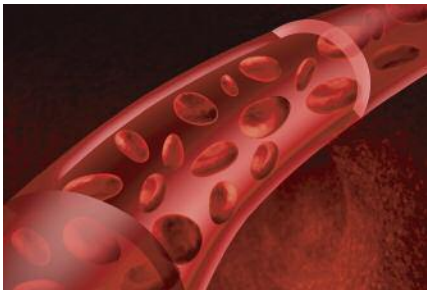
Research

Blood Test May Diagnose Alzheimer's

A blood test for antibodies produced in the immune system may potentially be used in the future to diagnose Alzheimer's disease in its early stage. Researchers at the Scripps Research Institute in Jupiter, Fla., compared six Alzheimer's patients with six healthy people and six Parkinson's disease patients and found three-fold more immunoglobulin (IgG) antibodies in all six Alzheimer's diseases. For the blood test study, researchers used thousands of synthetic molecules to screen antibodies and found two of them were able to capture high concentrations of IgG antibodies only in Alzheimer's patients. The blood test method, which was not based on the requirement of knowing the antigens that trigger the immune responses, could be potentially used to screen for biomarkers associated with other diseases as well. ❖

Research

Scientists Discover 600 Fat Species in Human Blood



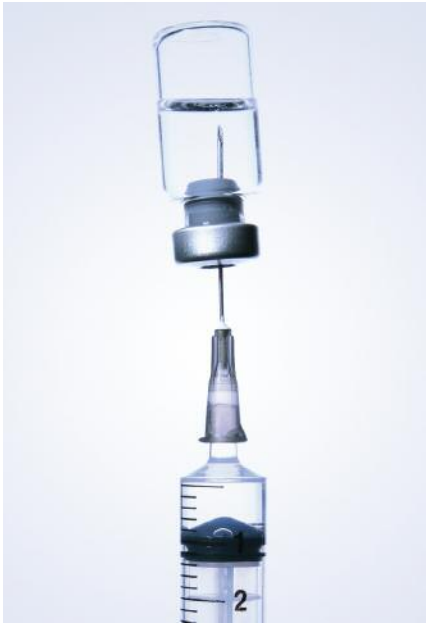
Scientists at the University of California, San Diego School of Medicine have created the first "lipidome" of human plasma, identifying and quantifying almost 600 distinct fat species circulating in human blood. The numbers and their diversity illustrate that lipids have key, specific functions, most of which are not yet recognized or understood, said Edward A. Dennis, PhD, principal investigator of the study. The findings were published in the November issue of the *Journal of Lipid Research*. ❖

Vaccines

Adults Fall Short on Vaccinations

While there has been some increase in adult vaccination rates, the Centers for Disease Control and Prevention reports that there is still room for improvement. About 40 percent of adults between the ages of 50 and 64 years, 33.4 percent of adults ages 19 to 49 in the high-risk group and close to 66 percent of adults ages 65 and older received the flu vaccine in 2009. The number of adults ages 65 years and older who received the pneumococcal vaccine rose to 60 percent from 50 percent in 1999, but only 10 percent of adults ages 60 and older received the shingles vaccine. And, the number of adults ages 19 to 49 who received the hepatitis B vaccine rose to 42 percent from 38 percent in 1999.

A National Foundation for Infectious Diseases (NFID)-commissioned survey found that 87 percent of 300 physicians polled said they talk about vaccines with every patient, but about 47 percent of 1,000 consumers surveyed said their doctors did not discuss vaccines other than the flu shot. According to NFID Medical Director Dr. Susan Rehm, nearly 90 percent of adults would get vaccinated if a doctor strongly recommended it, but just 50 percent know about the immunization schedule for adults. ❖



Research

Breakthrough Made in Cause of Encephalitis

Scientists at the Health Protection Agency in England have made a breakthrough in determining the causes of encephalitis, which affects approximately 700 people each year in the country, 7 percent of whom die from the disease.

In the study, researchers looked at more than 200 patients with encephalitis. In 63 percent of cases, the most frequent cause of the disease was the herpes simplex virus, which usually causes cold sores with no serious complications. However, they also found that almost 10 percent of all cases were caused by antibodies made by the body's immune system against certain brain proteins and not caused by infection. It was previously known that this could be a cause, but the frequency with which it occurred had not been established.

According to the researchers, the results show that drugs to "dampen down" the immune system are more likely to be required to treat encephalitis than previously thought, as brain damage is thought to occur through immune attack of the brain. The findings were published in *Lancet Infectious Diseases*. ❖

Research

'Master Switch' Identified in Inflammatory Diseases

Imperial College London scientists have identified a protein, called IRF5, that acts as a "master switch" in certain white blood cells that either stimulate or suppress inflammation. The findings suggest that blocking the production of IRF5 may help treat autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, lupus and multiple sclerosis. In addition, boosting IRF5 levels might help to treat people whose immune systems are compromised. The study was reported on in the journal *Nature Immunology*. ❖

FDA Approval

FDA Approves 60-Second HIV Test

The U.S. Food and Drug Administration (FDA) has approved a single-use rapid test that detects antibodies to HIV-1 in as little as 60 seconds. INSTI HIV-1, made by bioLytical Laboratories Inc., is designed for use with whole blood, finger-stick blood or plasma specimens and uses flow-through, rather than lateral-flow, technology to reduce processing time. The test also includes a "unique antigen construct" composed of recombinant proteins for HIV-1 (gp-41) and HIV-2 (gp-36).

FDA approval was based on clinical trial data showing minimum sensitivity and specificity of 88.8 percent and 99.5 percent, respectively, in finger-stick whole blood samples and 99.9 percent sensitivity and 100 percent specificity in venipuncture whole blood and plasma samples. As with all rapid HIV tests, positive findings must be confirmed before a diagnosis of HIV infection can be established.

The test previously was approved for use in 56 other countries, including Canada and member states of the European Union. ❖

Research

Use of Marijuana Increases Cancer Risk

Cannabis (marijuana) damages the immune system, increasing vulnerability to breast, bladder, lung and other tumors, as well as bacterial infections such as Legionnaires disease, according to a new study. Researchers at the University of South Carolina found that THC, the chemical behind the "high" of cannabis, fueled the production of a flood of cells thought to weaken the body's built-in defenses. In tests on mice, THC triggered the production of a "massive" number of immune cells called myeloid-derived suppressor cells (MDSCs), which normally act as a safety brake on the immune system, stopping its battle against disease from spiraling out of control. But, in the case of cancer, MDSCs make it easier for tumors to grow.

According to the researchers, the findings could have important implications not only for those who use the drug recreationally, but for those taking it to improve their health. Cannabis is used to ease the symptoms of multiple sclerosis, and it can also be used in treatment of cancer, glaucoma and HIV. However, a greater understanding of how to weaken the immune response could lead to new treatments for diseases caused by the immune system turning on the body. ❖

Research

Cancer Vaccine Acceleration Fund Is Launched by CRI

The Cancer Research Institute (CRI) has launched the Cancer Vaccine Acceleration Fund (CVAF), a new model of philanthropic investment and academic-industry collaboration to speed the clinical development of therapeutic cancer vaccines and other immune system-based therapies. Therapeutic cancer vaccines represent a new class of cancer treatment by harnessing the power of an individual's immune system's natural ability to recognize and attack cancer cells throughout the body. Clinical trials have provided evidence that therapeutic vaccines can help patients stabilize their existing cancers, achieve substantial tumor regressions and delay or prevent cancer recurrence, often with few to no side effects.

The CVAF, created in 2010, employs a highly selective screening process to identify and prioritize the most promising cancer vaccines and vaccine components in global development. It then seeks out partnerships with biopharmaceutical companies to bring these therapies into clinical trials, where they can be studied in-depth and where complementary immunotherapies can be identified.

To date, the CVAF has finalized collaborations with biopharmaceutical companies in support of the development of two immunotherapies and is reviewing several other companies with cancer vaccine candidates. In one of the collaborations, CRI provided up to $1.5 million in funding to Tolerx Inc. to support clinical development of TRX518, a first-in-class anti-GITR monoclonal antibody intended to enhance the immune system by enabling T cells to attack cancer cells more effectively. A Phase I clinical trial of TRX518 for melanoma patients is currently under way. ❖

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- IgA ≤25 mcg/mL

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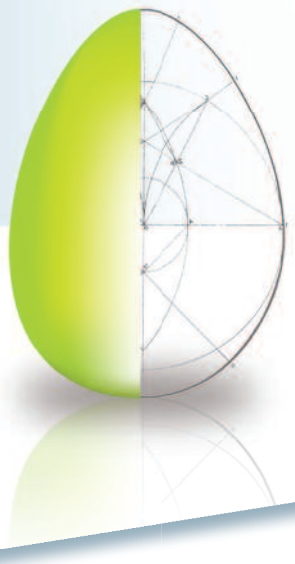
- In clinical trials, 97% of related adverse events were non-serious; 95% of 1038 infusions were administered without premedication. The most common adverse reactions were headache, pain, nausea, pyrexia/hyperthermia, fatigue, and chills
- 3-step virus inactivation/removal process, including nanofiltration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



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Important Safety Information

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

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

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

Privigen is manufactured by CSL Behring AG and distributed by CSL Behring LLC.
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www.CSLBehring-us.com **www.Privigen.com** 09-PVG-051 4/2010

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

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

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

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

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

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

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

1 INDICATIONS AND USAGE

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

1.1 Primary Humoral Immunodeficiency

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

1.2 Chronic Immune Thrombocytopenic Purpura

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

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

5.2 Renal Failure

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

5.3 Hyperproteinemia

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

5.4 Thrombotic Events

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

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

5.5 Aseptic Meningitis Syndrome (AMS)

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

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

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

5.6 Hemolysis

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

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

5.7 Transfusion-Related Acute Lung Injury (TRALI)

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

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

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

5.8 Volume Overload

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

5.9 Transmissible Infectious Agents

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

5.10 Monitoring: Laboratory Tests

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

5.11 Interference With Laboratory Tests

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Treatment of Primary Humoral Immunodeficiency

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

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

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

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

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

*Excluding infections.

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

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

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

* Two consecutive daily infusions.

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

6.2 Postmarketing Experience

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

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

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

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Use of Privigen in nursing mothers has not been evaluated.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Manufactured by:
CSL Behring AG
Bern, Switzerland

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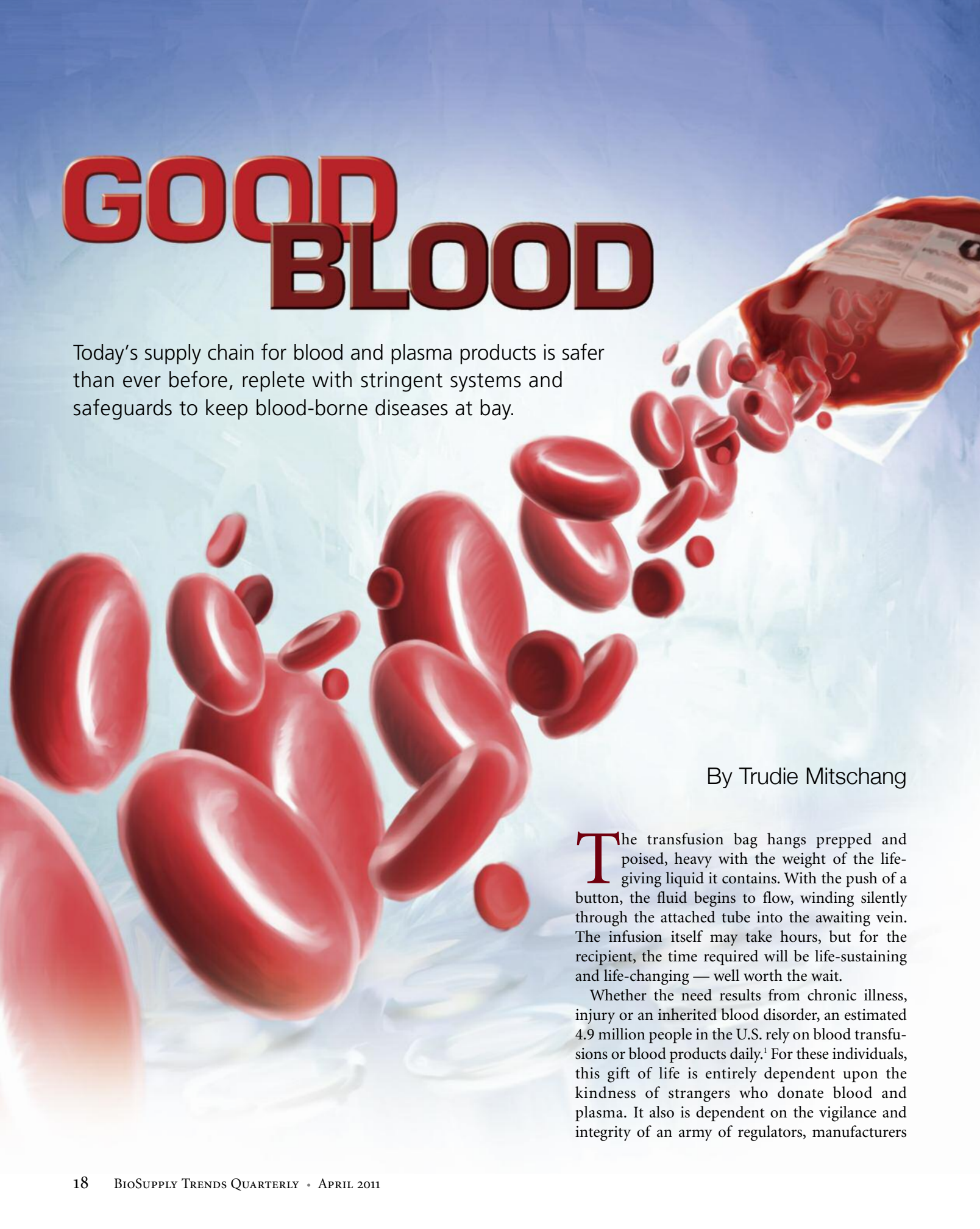
Kankakee, IL 60901 USA

Based on July 2010 revision.

GOOD BLOOD

Today's supply chain for blood and plasma products is safer than ever before, replete with stringent systems and safeguards to keep blood-borne diseases at bay.



By Trudie Mitschang

The transfusion bag hangs prepped and poised, heavy with the weight of the life-giving liquid it contains. With the push of a button, the fluid begins to flow, winding silently through the attached tube into the awaiting vein. The infusion itself may take hours, but for the recipient, the time required will be life-sustaining and life-changing — well worth the wait.

Whether the need results from chronic illness, injury or an inherited blood disorder, an estimated 4.9 million people in the U.S. rely on blood transfusions or blood products daily.[1] For these individuals, this gift of life is entirely dependent upon the kindness of strangers who donate blood and plasma. It also is dependent on the vigilance and integrity of an army of regulators, manufacturers

and health officials whose oversight for the past three decades has resulted in a blood supply that is safe, trustworthy and stringently screened for blood-borne diseases. According to the Centers for Disease Control and Prevention (CDC), the United States blood supply is currently considered among the safest in the world.[2] But this achievement did not come without a liberal dose of literal blood, sweat and tears.

Blood Safety in the Age of AIDS

The blood supply industry came under fire three decades ago when a new and deadly virus emerged, infecting thousands of patients, most in the hemophilia community. At the time, acquired immunodeficiency syndrome (AIDS) was an unknown disease, and therefore human immunodeficiency virus (HIV) antibodies were not yet a part of the blood supply screening process.

CDC statistics show that nearly all people infected with HIV through blood transfusions received those transfusions prior to 1985, the year HIV testing began for all donated blood.[3] The Public Health Service has since recommended an approach to blood safety in the United States that includes stringent donor selection practices and the use of screening tests. U.S. blood donations have been screened for antibodies to HIV-1 since March 1985 and HIV-2 since June 1992. The p24 antigen test was added in 1996. Blood and blood products that test positive for HIV are safely discarded and are not used. But even with these safeguards in place, questions and concerns still arise.

Ironically, the AIDS epidemic exposed how vulnerable the blood supply can be to new diseases. Yet it also served as a catalyst for industry improvement and reform.

In fall 2010, a documentary produced by Marilyn Ness titled *Bad Blood* stirred the blood safety controversy anew by chronicling the circumstances that led to HIV contamination in the nation's blood supply. Of course, finger-pointing is common in the aftermath of any tragedy, and accusations that more could have been done to prevent the infection of so

many may have merit. An analysis of the facts reveals that many factors combined to create this perfect viral storm. For one thing, there was widespread ignorance and fear surrounding HIV and AIDS. AIDS originally was considered a sexually transmitted disease, and initially, no one knew it could be spread by infected blood. In the early 1980s, blood banks were already taxed by diminished supplies, and bad publicity about blood safety had the potential to discourage donations at a time when they were desperately needed. For that reason, blood banks did not immediately rush out with news of the infected blood supplies. Then, there was the political climate. The early '80s saw a shift toward conservative ideology that promoted the benefits of smaller government and reduced regulation, leaving many health agencies woefully understaffed — and unprepared — for an epidemic of this magnitude.

In the end, it was simply impossible to predict the devastation of the AIDS outbreak; nearly 10,000 people with hemophilia were infected with HIV between 1978 and 1984.[4] In 1993, the Department of Health and Human Services asked the Institute of Medicine for an analysis of the tragedy. With 20/20 hindsight as an advantage, the study concluded that "a failure of leadership and inadequate decision-making processes" were pivotal. In particular, donor screening was not effective, regulatory action was weak, and hemophiliacs were not well-enough informed about the risks.[5]

In a recent leadership profile in this publication, Victor Grifols, Grifols S.A. president, spoke of the ongoing controversy:

"Even 30 years later, we are still learning the lessons from the AIDS outbreak in the 1980s. It is a history that we still have to address. We can say with certainty that the blood and plasma supply chain is much safer today than it was 50 years ago. But, this is an evolving field. We can also say with certainty that the field will be safer 50 years from today. Safety is a never-ending pursuit."

Ironically, the AIDS epidemic exposed how vulnerable the blood supply can be to new diseases. Yet it also served as a catalyst for industry improvement and reform. Doctors began making more informed choices about recommending transfusions. Scientists began devising improved methods for disease testing and virus inactivation. Manufacturers, too, developed better testing and screening protocols. Positive changes emerged on the heels of disaster.

Of course, the fact that HIV and other viral contaminants appear to be under control doesn't mean that manufacturers, healthcare providers or consumers can relax and disregard old safety concerns. As the focus on safety continues to evolve, everyone involved in the process is tasked with proactively expanding safety guidelines to keep history from repeating itself and protect the blood supply from new threats.

Safety at the Manufacturing Level

Patients who need blood transfusions or infusions of blood plasma products often have few options when it comes to being selective about the product they receive, typically leaving such decisions in the hands of their healthcare providers. Still, it is the ultimate act of faith to merge someone else's life blood with your own, with no knowledge of the donor's personal habits, health history or background. As a patient, you simply trust that the products have been adequately screened and processed prior to being administered. And few patients are aware of just how lengthy and involved that screening process is.

"Over the last 25 years, pharmaceutical manufacturers have implemented extensive safety protocols in collecting and producing plasma products," says Christopher Healey, vice president, government and public affairs, Grifols Inc. "No longer is plasma collected from high-risk populations — all donors are carefully screened, all donations are tested, and all plasma-derived products are virally inactivated."

Over a period of years, the FDA has progressively strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products.

Healey goes on to explain that donor screening and testing are only the first steps in the complex manufacturing process for blood and plasma products. Although manufacturers use plasma only from donors who have been screened and test negative for the presence of common viral pathogens, each individual plasma product is subjected to multiple purification viral inactivation and removal processes. The type of viral inactivation and removal methods used depend on the plasma product, but common viral inactivation methods include:

- Solvent detergent treatment that consists of adding a soap-like chemical to the plasma that breaks down and destroys the fatty coating surrounding lipid-enveloped viruses. By destroying this fatty coating, the viruses are also destroyed.
- Heat treatment that involves heating each product vial to 80 degrees Centigrade for 72 hours. The temperature is carefully controlled to maintain it at a level that is effective against pathogens but not damaging to the therapeutic proteins.
- Nanofiltration that allows the wanted therapeutic proteins to pass through a specially designed membrane with a reduced pore size, while other particles or pathogens are trapped and discarded.

These are validated procedures that have proven to be effective at eliminating a wide array of potential contaminants such as bacteria and viruses, including hepatitis, HIV and many others. It's notable that there have been no cases of HIV or

if you spot it, you can stop it

Name: Joseph Miller Age: 62 years

Model is used for illustrative purposes only.

Symptoms[1,2]:

- Arrives at the ER with spontaneous, severe gastrointestinal bleeding
- No prior history of bleeding

Labs[1,3]:

- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests and additional testing ordered by the attending physician

Treatments[1]:

- Did not respond to treatments, including platelets and fresh frozen plasma

Diagnosis: ACQUIRED HEMOPHILIA

Joe has acquired hemophilia (acquired inhibitors), which can be very difficult to diagnose and is **fatal in more than 20% of all cases**.[4]

You can help patients like Joe by being aware of the red flags of acquired hemophilia and bringing them up to the physician.

When you see an unusual order of factor VIII (FVIII), ask some simple questions:

- What is the reason for your recent unusual order of FVIII?
- Do you have a patient with congenital hemophilia?
- Is bleeding under control?
- What diagnostic tests, such as an aPTT or a mixing study, have been performed?
- Was the aPTT prolonged?
- Have you consulted a hematologist?
- Have you considered acquired hemophilia?

Find out more about acquired hemophilia and treatment at **CoagsUncomplicated.com/Joe**.

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Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540 U.S.A.

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Types of Blood Products

Blood is an amazing and complex material. Different components of blood are used for a myriad of products and treatments.

- **Whole blood:** This is blood in its natural state. It consists of red cells, white cells, platelets and plasma. Whole blood is rarely used in a medical setting, except in instances of massive blood loss.
- **Red blood cells:** These vital cells carry oxygen and are used to treat anemia, provide oxygen to tissues and replace blood lost during surgery.
- **White blood cells:** These hard-working cells protect the body against infection. White blood cells provide stem cells for transplantation.
- **Platelets:** These are the sticky cell fragments that help blood clot. Platelets are used to control bleeding caused by platelet deficiency, including treatment for leukemia and other types of cancer.
- **Plasma:** This is the fluid portion of blood that carries proteins, salts and nutrients. Plasma is used to control bleeding caused by low levels of clotting factors.
- **Cryoprecipitate:** A product derived from plasma, cryoprecipitate is used to control bleeding and treat hemophilia and other bleeding disorders.
- **Concentrated plasma proteins:** These are derived from plasma and are used to treat genetic diseases, dissolve blood clots and protect against certain infectious diseases.

hepatitis transmission via plasma medicines since the implementation of such validated viral inactivation methods in the early 1990s. An important distinction is that plasma products can be virally inactivated while blood cannot, and it relies wholly on donor screening and testing. Additionally, the Internal Quality Plasma Program (IQPP), which was adopted by U.S. plasma companies, exceeds the Food and Drug Administration's (FDA) screening requirements. IQPP guidelines include the exclusive use of repeat donors, 60-day inventory holds and nucleic acid testing (NAT) for each donation. Procedures such as these have been incorporated industry-wide in an effort to maximize plasma product supply chain safety.

In its *2010 Corporate Responsibilities Report*, global specialty biopharmaceutical company CSL Behring notes that for plasma-derived therapies, the most important safety issue is the potential for contamination with pathogens that originate from the plasma itself. The company adds that while the theoretical risk of pathogen transmission can never be zero, it consistently utilizes multiple and overlapping safety measures to reduce contamination risk to as low as is technically feasible.

"CSL Behring and its subsidiary, CSL Plasma, maintain an unwavering focus on safety that is driven by an integrated system of safety across four critical areas of operation: selection of plasma, manufacturing of plasma-derived products, quality control and monitoring," says Albrecht Gröner, PhD, CSL Behring's director of preclinical R&D–pathogen safety. "In the event that pathogens enter the manufacturing pools from quality controlled plasma, which is a very low probability, we have effective and robust pathogen inactivation and removal steps in place, including pasteurization and nanofiltration. These processes ensure a final product with a strong margin of safety."

The Complex Relationship Between Patients and Donors

Blood donation and plasma donation meet very different and essential needs, and both are vital to the healthcare system. Blood and plasma donors come from all walks of life and donate for many reasons. All are paid for their services, but not all donors are motivated by monetary gain.

Coni Dutka, a retired educator and longtime blood donor, recently began donating plasma after learning there was a great need for the colorless watery fluid that is the key ingredient for many products crucial to treating the chronically ill. Patients suffering from a host of life-threatening conditions, including hemophilia, shock or trauma, immune deficiencies and other blood disorders, benefit from plasma.

After undergoing the intensive plasma donor screening process, Dutka, 62, became curious and began researching what happened to her plasma once the donation was completed. What she learned was eye-opening. "I had the opportunity to visit a well-known fractionation plant and watch the detailed process up close," says Dutka. "Observing how many safety steps were involved was very impressive. I also had the chance to meet some of the patients who benefit from my donations. That's when I realized that donating plasma is similar to donating an organ because something from my body is going into someone else's body and giving them life."

The Internal Quality Plasma Program (IQPP), which was adopted by U.S. plasma companies, exceeds the Food and Drug Administration's (FDA) screening requirements.

Kris McFalls, the mother of two children who have depended on plasma-derived intravenous immune globulin (IVIG) for

the past 20 years, says that the goodness and generosity of plasma donors and the vigilance of blood product manufacturers is something she never takes for granted. "Safety is always a concern for us. No amount of contamination is acceptable when lives are at risk," says McFalls. "I have seen the manufacturing process with my own eyes. I know each and every employee takes their job very seriously. Nothing is left to chance, and higher-than-required standards are used. I feel quite confident my kids' safety is taken into account with each and every step of the donation and manufacturing process."

In 2009, McFalls toured the Talecris Biotherapeutics manufacturing plant in Clayton, N.C. The company hosts its "Up Close and Personal Patient Open House" event annually, and patients are invited to observe various aspects of the complex manufacturing process. Talecris, like other plasma and blood product manufacturers, is held to universally stringent FDA guidelines for sterility and safety — standards that afford patients and caregivers of those with chronic illness much-needed peace of mind. "Taking that tour gave me comfort because I saw firsthand the care and pride put into manufacturing life-saving medications like immune globulin," McFalls says.

The FDA's Role in Blood Product Safety

Over a period of years, the FDA has progressively strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products. For one thing, blood donors are now asked specific and very direct questions about risk factors that could indicate possible infection with a transmissible disease. This "upfront" screening eliminates approximately 90 percent of unsuitable donors, and is a marked departure from screening processes in the '80s, when it was considered inappropriate to ask about a donor's sexual preference or drug habits. In addition, the FDA requires blood centers to maintain lists of unsuitable donors to prevent the use of collections from them. Last, all blood donations are routinely tested for seven different infectious agents.[6]

In addition to more stringent screening guidelines, the FDA has significantly increased its oversight of the blood industry as a whole. FDA inspects all blood facilities at least every two years, and "problem" facilities are inspected more often. And, blood establishments are now held to quality standards comparable to those expected of pharmaceutical manufacturers.

With so many safeguards in place, is it safe to say the nation's blood supply is 100 percent infection-free? Unfortunately, as biological products, blood and blood products are likely always to carry an inherent risk of infectious agents, which means zero risk may be unattainable. Still, statistics show that in 1995, the risk in the U.S. of HIV-1 transmission per blood unit transfused was estimated to be between one in 450,000 and one in 660,000. By 2003, this estimated risk had decreased to between one in 1.4 million and one in 1.8 million units, with new and improved safety and screening methods continually on the horizon.[7]

While a blood supply with zero risk of transmitting infectious disease may not be possible, the blood supply today is safer than it has ever been. The role of regulatory agencies, blood banks and blood product manufacturers remains to drive that risk to the lowest levels achievable without unduly decreasing the availability of this life-saving and life-giving resource. ❖

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

Blood Supply Fast Facts

- People over the age of 65 use 43 percent of all donated blood. The demand for blood and blood products is expected to increase as the population ages.
- Twenty-five percent of all blood products are used to treat cancer patients.
- One out of every 10 people entering a hospital requires blood.
- Severe burn victims can need the platelets from about 20 blood unit donations during their treatment.
- The average liver transplant patient needs 40 units of red blood cells, 30 units of platelets, 20 bags of cryoprecipitate and 25 units of fresh frozen plasma.
- People who have been in car accidents and suffered massive blood loss can need transfusions of 50 or more units of red blood cells.

Source: American Red Cross. 50 Quick Facts. Accessed at www.givelife2.org/sponsor/quickfacts.asp.

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Introducing

Flebogamma®10%DIF

Immune Globulin Intravenous (Human)

Shaping the future

Highly purified IGIV

- Trace amounts of IgA: <0.006 mg/mL [1] (specification value: <0.1 mg/mL)
- Very low sodium content
- Sorbitol stabilized

Demonstrated benefits in replacement therapy

- In the pre-approval clinical trial: [2]
  - 0.025 serious bacterial infections/patient/year
  - Well tolerated: Does not put patients at increased risk for any adverse events other than those that could be reasonably expected in primary immune deficiency patients who are receiving an infusion of intravenous immune globulin

Broad pathogen safety margin

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

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

(1) Data on file, Instituto Grifols, S. A.
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- Liquid
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- Three presentations: 5, 10 and 20 gram vials

Enhancing our commitment to you

- Every vial is laser etched with its own unique identifier number*, which helps to deter tampering and counterfeiting
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* Laser etched identifier number may at times be covered by the label.

Important Safety Information

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

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

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

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

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

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

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

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

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

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

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

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

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

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

See the difference today

FDA04-1-US-10

GRIFOLS

Immune Globulin Intravenous (Human)
Flebogamma® 10% DIF
For intravenous use only
RX only

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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

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

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

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

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

WARNINGS AND PRECAUTIONS

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

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

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

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

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

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

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

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

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

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

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

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

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

Post-marketing Experience

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

DO NOT FREEZE.

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

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

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ACOs: Reducing Costs While Improving Quality of Care

By Ronale Tucker Rhodes, MS

With the push to reduce the skyrocketing cost of healthcare yet improve the quality and efficiency of care, Accountable Care Organizations, part of the new healthcare reform bill, could be one solution.

As debate over healthcare reform rages on, those who oppose the Patient Protection and Affordable Care Act enacted in March 2010 argue that it does not address the issue of rising healthcare costs. According to the Kaiser Family Foundation, the U.S. government spent more than $2.3 trillion on healthcare in 2008, averaging $7,681 per person, which is more than three times the $714 billion spent in 1990. That amount is twice as much as what is spent on food, says the McKinsey Global Institute, despite the fact that the prevalence of disease is relatively less than that in comparable countries. Add to this the rising cost of health insurance premiums (an increase of 131 percent for employer-sponsored health coverage since 1999), and one can see that healthcare expenditures are indeed a significant issue.[1]

While proponents of the healthcare reform bill agree that it doesn't directly address the core issues of rising costs, they argue it's a start; it expands benefits and provides coverage to millions of people who were previously unable to get it. And, it does contain one provision that aims to both decrease healthcare spending and increase the quality and efficiency of care: Accountable Care Organizations (ACOs).

What Is an ACO?

ACO is a phrase attributed to Dr. Elliot Fisher, director of the Center for Health Policy Research and a professor of medicine at Dartmouth Medical School. For the past 30 years, Dr. Fisher has led the Dartmouth Atlas Project, which focuses on the quality of healthcare, as well as its cost, and the relationship between the two. Findings from the project illustrate wide variations in the cost of care across the country, and that the regions that spend more per patient don't necessarily obtain better outcomes. In response to these findings, Dr. Fisher came up with the idea for ACOs as a "locus for shared accountability" for a patient's healthcare.[2]

Introduced as one of Medicare's pilot programs in the healthcare reform bill, "an ACO is a network of doctors and hospitals that shares responsibility for providing care to patients." The ACO would be responsible for coordinating all of a patient's healthcare services (primary care, specialists, hospitals, home healthcare, etc.) to ensure the best quality of care. Providers in the ACO would be jointly accountable for the health of their patients, which would give them incentives to cooperate and save money by avoiding unnecessary tests and procedures. What's more, providers do not have to be in the ACO's network; patients are free to go to the provider of their choice.[3]

Dr. Thomas Lee, associate editor of *The New England Journal of Medicine (NEJM)* and network president of Partners Healthcare, says in a video roundtable of *NEJM on ACOs* that what's hoped for "is a delivery system that delivers higher-quality care more efficiently." Speaking in the roundtable, Dr. Fisher says that ACOs should have three key attributes: organized care, performance measurement and payment reform, which when aligned support physicians in their efforts to improve care.[4]

How Will ACOs Be Formed?

In January 2012, a pilot program will be established by the Centers for Medicare & Medicaid Services (CMS) to give groups of Medicare providers the opportunity to form a qualified ACO. To facilitate ACO formation, the secretary of the U.S. Department of Health & Human Services (HHS) is authorized to waive statutes and regulations that currently inhibit physician-hospital integration.

In CMS' pilot, the types of qualifying providers include physician group practice arrangements, networks of practices, hospital-physician joint ventures and hospitals employing physicians and other clinical professionals. To participate, providers must agree to become accountable for the overall care of their Medicare fee-for-service (FFS) beneficiaries, participate for a minimum of three years, have a legal structure enabling it to receive and distribute bonuses, provide information on physicians practicing in the ACO, have a management and leadership infrastructure in place, define processes to promote evidence-based medicine and patient engagement, and meet patient-centeredness criteria determined by the HHS secretary.

Introduced as one of Medicare's pilot programs in the healthcare reform bill, "an ACO is a network of doctors and hospitals that shares responsibility for providing care to patients."

Key competencies of an ACO also are required, including clinical, financial and operational buy-in; a patient-centric culture; a highly integrated delivery system; an IT infrastructure to support care coordination and population health management; a system for monitoring, managing and reporting quality; the ability to manage financial risks; a legal/management structure to allow for payment distribution and coordinated decision-making; a collaborative, transparent relationship with payer(s); reimbursement contracts that reward value rather than volume; and a process improvement system.[5]

How Will ACOs Operate?

An ACO would agree to manage all of the healthcare needs of a minimum of 5,000 Medicare beneficiaries for at least three years. The traditional fee-for-service system would remain in place; however, providers would be given bonuses to "keep costs down and meet specific quality benchmarks, focusing on prevention and carefully managing patients with chronic disease," as well as share in the savings when reducing costs below the predetermined benchmark.[3]

Quality benchmarks, which the ACO would be required to report on, will be established by the HHS. These will include measures of clinical processes and outcomes, patient experience and care, and utilization and costs.[5] Each ACO's cost benchmark will be based on the most recent available three years of per-beneficiary expenditures for Parts A and B services for Medicare FSS beneficiaries assigned to the ACO. And, these benchmarks will be adjusted for beneficiary characteristics and other factors, including the projected absolute amount of growth in national per capita expenditures for Parts A and B.[6]

An ACO that meets specified quality performance benchmarks will be eligible to receive a share (a percentage and any limits to be determined by the secretary of the HHS) of any savings every 12 months, if the actual per capita expenditures of their assigned Medicare beneficiaries are a sufficient percentage below their specified benchmark amount. There is no payment penalty if savings targets are not achieved.[6]

Bonuses will be awarded based upon how the ACO scores on the quality-of-care measures. Some prominent doctor and hospital groups are pushing for limits on how the quality of their care will be judged, as well as for bonus rules that will make it easier for them to be paid extra for their work, and to be paid quickly.[7] Dr. Fisher suggests providers "report regularly on performance measures that will reassure the public and payers that the quality of care is actually improving."[4]

What's Unknown?

There still are a lot of unanswered questions. While CMS indicated it would release its proposed ACO regulations, as of this writing, it has not. These regulations, which will likely be based on an open-door forum on ACOs that was held in June to gather provider input, will answer such questions, for instance, as how the quality-of-care measures will be judged and how beneficiaries will be assigned to ACOs, among a host of others. However, a CMS fact sheet does indicate that beneficiary assignment will be "invisible" to the beneficiary and will not affect his or her benefits or choice of physician.[5]

Other unknowns include both legal and economic concerns. Many in the healthcare industry have raised concerns that ACOs could run afoul of antitrust and anti-fraud laws, which try to limit market power that drives up prices and stifles

competition. For instance, ACOs in rural markets could potentially grow so large that they would employ the majority of providers in a region. The Federal Trade Commission says it's trying to clarify antitrust guidelines for ACOs, and the U.S. Justice Department's antitrust division has offered to provide an expedited antitrust review process for ACOs. There also is concern that ACOs could accelerate hospital mergers and provider consolidation. But Steve Lieberman, a visiting scholar at the Engelberg Center for Health Care Reform at the Brookings Institution and the president of Lieberman Consulting Inc., says that's already "such a powerful and pervasive trend that it's a little like worrying about the calories I get when I eat the maraschino cherry on top of my hot fudge sundae. It's a serious public policy issue with or without ACOs."[3]

Who Is Moving Forward?

Despite the fact that ACOs are intended as a Medicare pilot program under the healthcare reform bill, many states, insurers, hospitals and providers in the private sector are moving ahead with them.

In January, the New Jersey Senate Health, Human Services and Senior Citizens Committee approved a bill that would enable five groups of medical professionals and managed care companies that treat at least 5,000 Medicaid patients to form an ACO. The bill, which is on the heels of six ACOs formed by hospital and physician practices in the past year in New Jersey, will serve low-income patients in one concentrated area who rely on the state's $9 billion Medicaid program.[8]

Some of the largest health insurers in the country, including Humana, United Healthcare and Cigna, have announced plans to form their own ACOs, saying they can play an important role in ACOs because they track and collect data on payments, a critical component to coordinating care and reporting on results. Even large hospital systems are buying up physician practices with the goal of becoming ACOs that directly employ the majority of their providers. Hospitals, which have greater access to capital, could have an easier time financing the initial investment required to start an ACO.[3]

An ACO would agree to manage all of the healthcare needs of a minimum of 5,000 Medicare beneficiaries for at least three years.

In the private sector, both Premier, a healthcare alliance, and the Brookings Institute are working with hospitals to develop ACOs. The Premier ACO collaborative was launched in May and has two tracks. The first is an implementation cohort that has developed the foundational elements necessary to execute an ACO strategy. The second is a readiness cohort designed to help health systems develop the foundational elements. Beginning this summer, organizations that are part of this cohort will participate in learning events and receive support to develop the infrastructure and collect population-based health metrics. The Brookings Institute, in conjunction with the Dartmouth Institute for Health Policy, is working with three providers to create organizations that are locally accountable for population health and share in savings generated from an "intervention"-based healthcare system to a "prevention"-focused system.[5]

And, in some areas of the country, including parts of California, large multispecialty physician groups are looking to become an ACO on their own by networking with neighboring hospitals.[3]

Are There Examples to Learn From?

According to Dr. Fisher, there have already been a number of pilots run by Medicare over the last five years, which are part of the Physician Group Practice Demonstration. These pilots are essentially the ACO model with a slightly different benchmarking approach. One of the pilots is Norton Healthcare, which in partnership with Humana has signed an ACO contract for its under-65 population. "The physicians at Norton are working hard with the hospital to pull themselves together, reorganize care, figure out how to work with Humana to get really useful, timely data that helps them know how their patients are doing and how to improve their care," says Fisher. "So, there is actually quite an elegant partnership between the payer and the provider. Instead of dickering over prices, they are trying to work together to say, 'How can we jointly improve care?'"[4]

But, Dr. Gail Wilensky, an economist and senior fellow at Project Hope, who served in a variety of roles relevant to this topic, including administrator of the Health Care Financing Administration and chair of MedPAC, and who also participated in the *NEJM* roundtable, says she is dubious about ACOs precisely because of what is happening with the Physician Group Practice Demonstration. "These were 10 set-up cases, in the sense that if anybody should be able to produce savings with quality, it ought to have been the 10 groups that came into this demo," says Wilensky. "What to me was the most impressive is that while all of them were able to meet the quality goals, in the initial year only two of them were able to produce savings at a level that would

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- Pasteurized to inactivate viruses, with no confirmed cases of virus transmission
  - Thrombate III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob disease agent that can cause disease
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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
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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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allow them to share some savings. And, even after three years, only five of them have been able to do that." However, Wilensky does add that in no way is she saying she doesn't want to see ACOs go forward because "we've got to get away from where we are, which is a reimbursement system that rewards for more and more complex, that's fragmented, that's stovepipe."[4]

Despite the skepticism by some, there are some quantifiable success stories. In February, members of the Healthcare Leadership Council (HLC), a coalition of chief executives from the nation's premier healthcare companies and organizations, presented the *HLC Value Compendium* to CMS Administrator Dr. Donald Berwick. The publication offers 26 current examples, with supporting metrics, of ways in which the private sector is currently improving healthcare quality, efficiency and safety. In producing the document, HLC leaders said they wanted to provide case studies that could help jump-start federal efforts to improve healthcare delivery.

In the publication, there are examples of significant strides in improving U.S. healthcare from hospitals, integrated delivery systems, pharmaceutical companies, medical device manufacturers, group purchasing organizations, insurers, distributors and other key players in the healthcare continuum. In addition, it highlights successes with innovative payment methods, beneficiary engagement models, visionary use of health information technology, cutting-edge medical devices that optimize care, and new service-delivery approaches.

There is also a study published in January in the *Journal of Ambulatory Care Management* that concluded that a San Antonio ACO with a network of patient-centered medical home clinics, but no hospital, is providing comprehensive, high-quality and efficient healthcare services that improve patient care and outcomes.

Titled "Case Study of a Primary Care-Based Accountable Care System Approach to Medical Home Transformation," conducted at the Robert Graham Center for Policy Studies, the study looked at the organization and services provided between 2000 and 2008 by WellMed Medical Group, which has more than 87,000 patients and plan members. Researchers focused on Medicare Advantage patients, many of whom have complex health conditions, such as diabetes, congestive heart failure, ischemic heart disease, chronic obstructive pulmonary disease and asthma, who were receiving care at 21 WellMed Group practices in San Antonio. Over the past 20 years, WellMed developed a care model that meets 97 of the 100 elements that define a patient-centered medical home, according to the National Committee for Quality Assurance guidelines. It also has well-developed disease and complex care management programs, health coaches and close monitoring of quality.

The study found that "WellMed improved preventive care for the conditions that we measured and achieved remarkably high guideline compliance for diabetes and blood pressure. Their mortality rates remain well below the state average."[9]

Only Time Will Tell

For ACOs to work, they will need to seamlessly share information. And, this will require a great deal of planning and investment. According to Lieberman, "ACO has become the three-letter health acronym of the year, if not the decade." Unfortunately, he says, the health industry tends to operate with a "kind of a herd behavior," rushing to implement an idea "without working through the detailed business questions of how they'll work."[3]

Only time will tell. But, our current fragmented system incentivizes providers to offer neither cost-effective nor coordinated care.[2] "Given the state of the U.S. healthcare system, the risk of inaction — perpetuating year-over-year increases in cost coupled with incremental improvements in quality — is the greatest risk a provider faces. ACOs offer one potential solution to these challenges."[5] ❖

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

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Promoting Adherence to Therapy

With options ranging from new web-based applications to electronic medication reminders, physicians may need to think outside the pillbox when it comes to encouraging medication adherence.

By Trudie Mitschang

Like leading the proverbial horse to water, physicians can write a prescription for treatment, but they have limited control over patient follow-through. This is not only frustrating for doctors and detrimental to patients, it also places an economic burden on our healthcare system. A new report conducted by the New England Healthcare Institute (NEHI) found that not taking medications as prescribed leads to poorer health, more frequent hospitalization, a higher risk of death and as much as $290 billion annually in emergency room visits and other avoidable medical expenses in the United States.[1] Non-adherence also causes 125,000 deaths annually and between 10 percent and 25 percent of hospital and nursing home admissions.[2] With such dire consequences, it begs the question: Why would a patient resist treatment knowing it could ultimately prolong illness or delay recovery? Unfortunately, there are no simple answers, nor is there a one-size-fits-all solution.

Understanding Non-Adherence

Studies show that when patients admit to non-adherence, the most common excuses include fear of unpleasant side effects, cost of medication, confusion about instructions, forgetfulness, language barriers and feeling "too good" to need medicine. Surprisingly, those with chronic conditions like diabetes and high blood pressure are among the groups that are least likely to follow their medication regimen. A recent report by the World Health Organization (WHO) revealed that 50 percent of patients with chronic disease do not take their medication as prescribed.[3] In response, some organizations like NEHI are urging the federal government to make the issue a part of the national healthcare reform debate.

"If physicians and other care providers are reimbursed for better health outcomes, we believe that will go a long way toward driving adherence, because providers will have incentives to invest in the time and resources and counseling and technology and other tools that are really needed to educate patients and, in some cases, to change their behavior and to really move the needle on adherence," NEHI Executive Director Valerie Fleishman told the *Boston Globe* in a recent interview.

Lack of coordination of care also can be a factor affecting medication adherence. Patients with coexisting conditions may take multiple medications prescribed by different physicians, creating a level of complexity the patient may not be equipped to handle, and a need for a level of case management that is typically not available. To adequately address this need, a physician would likely need to invest substantial time and effort gathering information and data and/or utilize electronic record sharing, which is currently not widely available within the U.S. And without the reimbursement incentives mentioned earlier, physicians with busy caseloads are unlikely to be motivated to spend a lot of time and effort compiling such data.

Pursuing a Multipronged Solution

Medication non-adherence can take a variety of forms, including not having a prescription filled, taking an incorrect dose, taking a medication at the wrong time, forgetting to take doses, or stopping therapy too soon. In understanding the full scope of the problem, it's important to note that medication non-adherence is not the only form of non-adherence impacting patient outcomes. Patients can also suffer when they avoid making recommended lifestyle changes, such as dietary improvements, exercise or smoking cessation. Others may neglect nonpharmacologic interventions, such as physical therapy. Because the problem is more complex than simply convincing someone to take a pill at prescribed intervals, a successful solution will require a multipronged approach. A look at some of the integrated healthcare delivery systems that are effectively implementing this type of approach could provide a glimpse into how other stakeholders might tackle the issue. Community Care of North Carolina (CCNC), Geisinger Health System in Pennsylvania and Group Health Cooperative in Washington state and Idaho are three organizations that are already making inroads.[4]

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CCNC, a loose affiliation of 14 physician networks serving Medicaid and uninsured patients, has launched the Pharmacy Home Project, a plan that pays participating physicians a monthly fee for coordination of care. Adherence is promoted through the use of case managers, who are embedded throughout the networks, and clinical pharmacists, who serve multiple physician practices on a rotating basis. The program also collects data on patient medications from multiple sources, including medical charts, claims records and records of prescriptions filled to provide prescribers with complete and accurate data. Under this program, CCNC has achieved a 5 percent to 7 percent increase in adherence rates.

At Geisinger, each patient's medication preferences are gathered via electronic survey prior to their physician appointment. This simple step streamlines doctor visits and makes follow-up easier. Geisinger also has a medical homecare model that requires nurses to actively follow up with patients to monitor medication use and answer questions or concerns, giving patients one less excuse for skipping their medications. The organization also has made changes to its own employee health benefits by reducing copayments and deductibles for medications for chronic conditions. Geisinger reports that it has reduced monthly costs as much as 7 percent.

Group Health Cooperative provides an extra layer of patient-centered support, employing nurse case managers who work closely with patients to encourage medication adherence. Case managers also focus on patient education

and troubleshooting that includes sourcing more affordable options for prescriptions. The Group Health Cooperative reports that the results have included annual savings — representing avoided healthcare costs — of more than $476 per participant.

All of these organizations have been successfully leveraging information technology and patient data, while focusing on customized interventions tailored to patients' individual needs. They also offer trained follow-up care designed to improve adherence. While these models do not address all of the issues involved in non-adherence, they do offer encouragement that cost-effective strategies are available.

Innovative Medication Management

Implementing technology platforms for patients and providers has the potential to dramatically improve patient outcomes and adherence. A recently published study in the *American Journal of Managed Care* revealed that health management technology promotes medication adherence, and that electronic health records are an effective and low-cost method of ensuring that patients remember to take their prescribed medicine.[5] Researchers from CVS Caremark and Brigham and Women's Hospital, Harvard University, collaborated over a period of three years to review medical journal articles on the impact of technology. They examined more than 7,000 papers published between 1966 and 2010 that discussed the use of healthcare management technology on disease management efforts, particularly for patients with diabetes and cardiovascular disease. In a statement published Dec. 28, 2010, senior author William H. Shrank noted: "This review suggests that health information technology interventions are promising tools in the fight to improve medication adherence. While there have been many studies on the subject of boosting adherence, we were surprised to find so few on the topic of using health information technology to accomplish this goal."

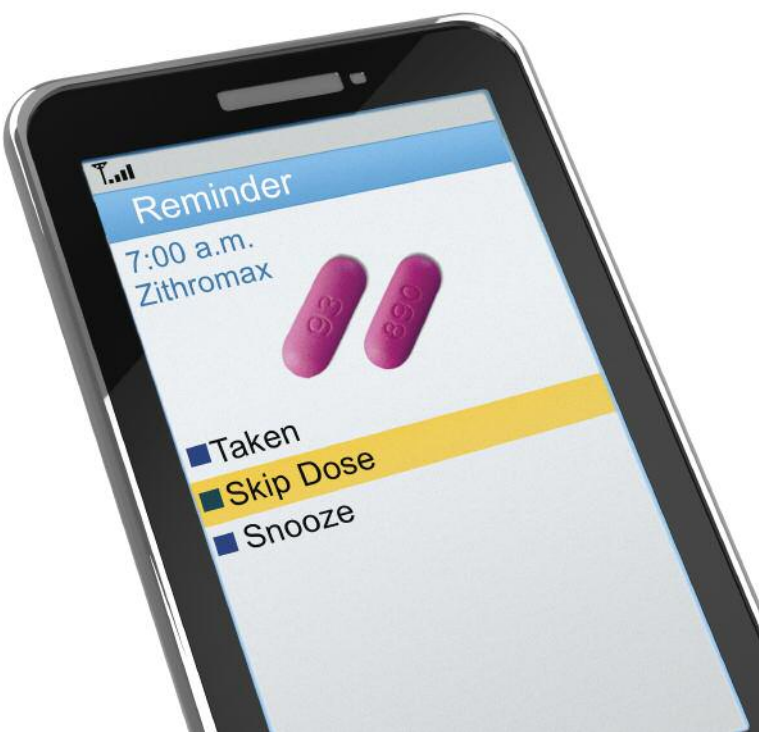
Implementing technology platforms for patients and providers has the potential to dramatically improve patient outcomes and adherence.

From cell phone apps to texting bottle caps, savvy inventions are making medication adherence easier for practitioners and the patients they treat. Electronic Medical Software, which is used to track patients' follow-up activity, adherence and progress, also can set up clinical alerts to notify the provider about drug interactions, allergies and other concerns. A notable feature of Electronic Medical Software, ePrescriptions also can boost adherence; for one thing, the prescription is transmitted directly to the pharmacy and is ready by the time the patient arrives. With ePrescriptions, the patient also receives detailed written instructions that can eliminate the confusion that sometimes sets in between the doctor visit and the prescription pickup.

Technology is making advances in hospital settings as well. In February of this year, LodgeNet Healthcare launched a new application for the hospital room that allows nurses to assign personalized patient video education based on diagnoses and medication treatment plans. The Assigned Education application is accessed via the television in a patient's room, and provides critical information about a patient's illness, medication and discharge instructions.

Wireless health tools and services are becoming increasingly popular ways of helping people follow their medication regimens. The Pill Phone, a patented mobile medication reminder software that is available on many wireless phones, is the only wireless application to have FDA approval for medication management. The app acts as a comprehensive drug resource based on the best-selling guide *The Pill Book*, by Harold M. Silverman.

The TabSafe smart pillbox is another innovation making headlines. This gadget provides visual and auditory medication reminders and has been very popular among seniors in assisted-



living facilities. To use, patients press a button to dispense the correct pills and a text message is sent to predetermined recipients — perhaps a physician or family member — to confirm the pills have been dispensed.

GlowCaps by Vitality are the smart phone equivalent for prescription meds. These caps attach to standard pill bottles and connect to a cellular network. When it's time to take medication, they flash and play a sound. They also connect to wireless reminder light plugs and can call a phone. Additionally, they order refills when necessary and send a weekly report to the user and their doctor.

If you think smart bottle caps and texting pillboxes sound futuristic, how about "smart pills"? Sensor technology combined with intelligent medicine technology could serve as the ultimate solution to medication adherence issues in the near future. Proteus Biomedical has developed technology that actually can be embedded into pills; the company envisions a patient's physicians and caregivers will be able to confirm the medication was taken, and even track the patient's respiration, heart rate and body temperature from their mobile phones. Proteus expects the technology to be commercially available in the U.S. within the next three years.

For those with chronic illness, there are disease-specific adherence support tools. The FactorTrack Mobile App by Bayer HealthCare Pharmaceuticals is a customizable application for hemophilia patients that can be programmed to provide infusion reminders. The app also tracks and records infusions to provide streamlined recordkeeping. And, at NuFACTOR Specialty Pharmacy headquartered in Temecula, Calif., patients can log on to the company's website and access a menu of helpful tools tailored to the needs of patients requiring immune globulin infusions. Downloadable tools include an IG Treatment Tracker, Health Diary, Infusion Log and Medical Emergency ID Cards.

The Role of Communication in Adherence

For physicians, understanding the doctor/patient dynamic can go a long way toward improving adherence. The reality is, patients are not always completely truthful with their physicians and may avoid admitting they've missed or skipped medication dosages. The psychology behind this behavior lies in the way doctors are seen as authority figures; no one likes to be viewed as a "bad patient." To get around this hurdle, physicians might try the following communications techniques:

• Rather than asking if a patient has been taking medication as prescribed, ask how much medication they take and how frequently they take it; then compare the answer with the prescribed dosage.

• Provide clear instructions. Sometimes non-adherence stems from confusion. Speaking slowly and having the patient repeat back instructions can be helpful. Emphasizing how long a medication should be taken also is important.

• Ask if cost is an issue. Keep in mind a patient might be embarrassed to tell you that they cannot afford their medications. For patients with insurance, prescribing the first- or second-tier medications avoids large out-of-pocket expenses.

For physicians, understanding the doctor/patient dynamic can go a long way toward improving adherence.

• Discuss side effects. Detail the common side effects with the patient, addressing any fears they may have. Remind patients that the risks from active disease are higher than the adverse medication reactions.

• Touch on long-term positive benefits. Cost-effectiveness studies have demonstrated that staying on medications is ultimately cheaper than active disease; in today's economy that might be a motivating factor for some patients.

Adherence = Better Outcomes

Medication non-adherence is a pressing concern within the healthcare community, and one of the lesser-known issues impacting healthcare reform. Whether patients are tackling obesity, chronic disease or an infection requiring a course of antibiotics, encouraging adherence can produce better outcomes and literally save lives. And looking to the future, improving patient adherence to therapy will ultimately require updates in healthcare delivery models, investments in information technology systems and improved health plan designs focused on targeted, patient-centered care. ❖

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

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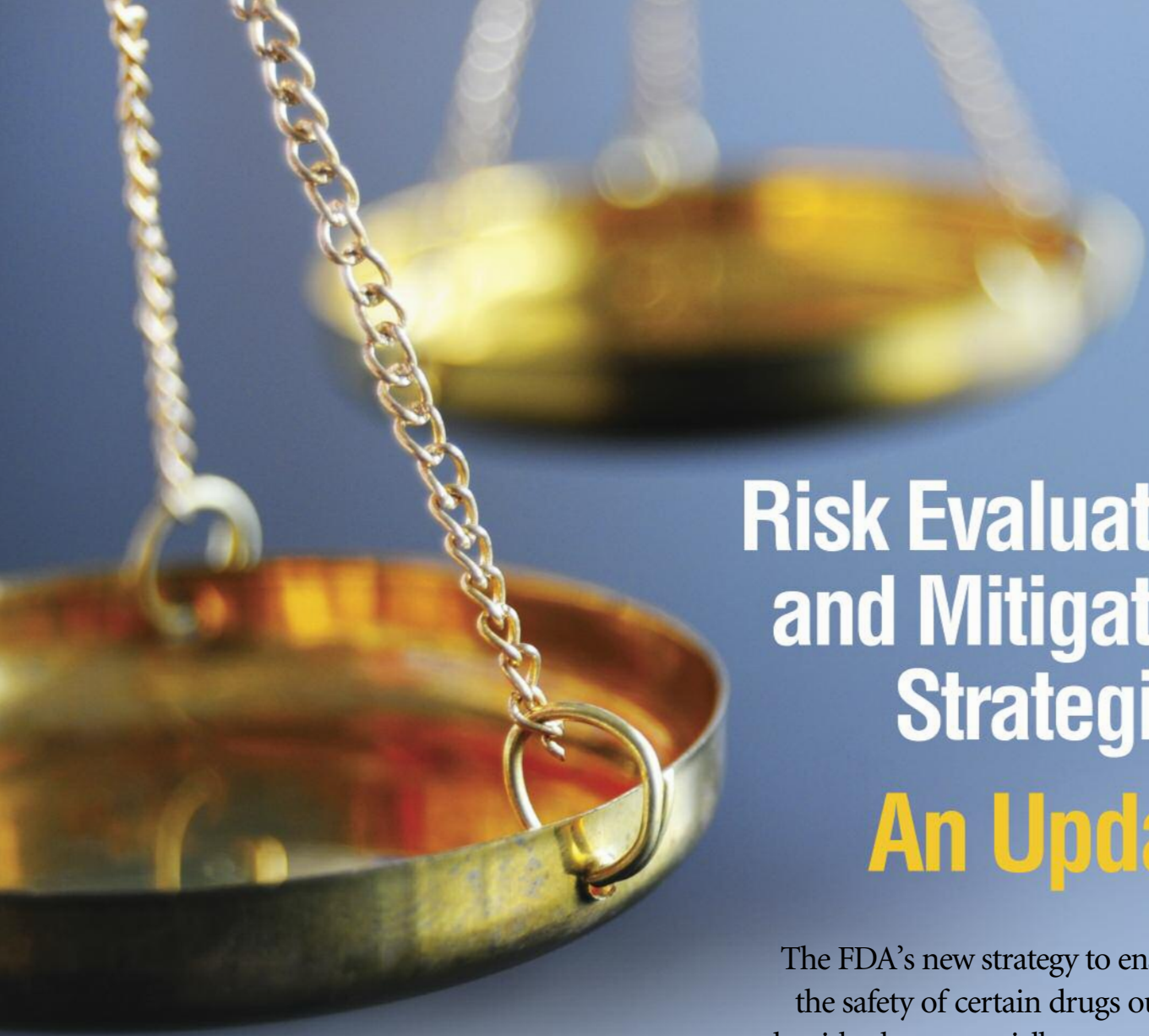

Risk Evaluation and Mitigation Strategies: An Update

The FDA's new strategy to ensure that the safety of certain drugs outweighs the risks they potentially pose to patients continues to evolve as the healthcare industry takes an active role in current and future REMS requirements.

By Ronale Tucker Rhodes, MS

The good news is that the abuse of illicit drugs in the United States continues to go down. The bad news is that more and more people are beginning to abuse "legal" prescription drugs. In fact, this is a fast-growing trend in the U.S. The National Institutes of Health (NIH) estimates that close to 20 percent of people over the age of 12 in the U.S., or 48 million people, have used prescription drugs for nonmedical purposes. Even more alarming is that the fastest growing demographic of prescription drug abuse is young people aged 15 to 24. The U.S. Department of Health and Human Services (HHS) reports that nearly three million teenagers and young adults (those aged 12 to 25) have become new abusers of prescription drugs. And, prescription drug abuse is rising among the elderly as well. Even though the elderly make up only 13 percent of the population, they account for about one-third of all prescriptions.[1]

The abuse of prescription medications is what led to the passage of the Food and Drug Administration Amendments Act (FDAAA), which took effect March 25, 2008. The Act authorized the FDA to require pharmaceutical manufacturers that submit New Drug Applications, as well as those that hold certain drug applications already approved, to submit a proposed Risk Evaluation and Mitigation Strategy (REMS).[2] As of this writing, there are more than 160 drugs with an FDA-approved REMS.[3]

But, it has been just three short years since the implementation of the FDAAA. And while the goals behind the program are more than worthy, there remains some question by patients, pharmacists, physicians and manufacturers about whether the current REMS requirements, as well as future requirements under discussion, are doing and will do what was intended.

What Are REMS?

REMS are being mandated to assess adverse risks associated with specific oncologic drugs, biologics and supportive care therapies. Depending upon the severity of the risks, the population likely to be exposed, as well as other factors, a drug may be required to have one or all components of a REMS program: 1) a medication guide or a patient package insert, 2) a communication plan for healthcare providers and 3) elements to assure safe use (ETASU).[4]

A medication guide contains information for patients on how to safely use a drug product. Most of the drugs that have FDA-approved REMS are required only to have this component of the program.

A communication plan involves risk communications to healthcare providers. The plan may include one or all of the following: 1) sending letters to healthcare providers, 2) disseminating educational information about the elements of the REMS to encourage healthcare providers to implement the components that apply to them or to explain certain safety protocols, and 3) disseminating information to healthcare providers through professional societies about any serious risks of the drug and any protocol to assure safe use.[5]

For REMS requiring ETASU, healthcare providers may be required to obtain and dispense the drug through specific distribution channels; possess specific training, education, experience or certifications in order to prescribe the drug; enroll patients in registry programs; and issue mandatory, time-sensitive reports of patient responses to treatment.[4]

What Are the Legal Implications of REMS?

The FDAAA grants FDA the authority to impose penalties on manufacturers that do not comply with REMS requirements. According to the FDAAA penalties section: "A responsible person who violates a REMS requirement is subject to civil monetary penalties of up to $250,000 per violation, not to exceed $1 million in a single proceeding. These penalties increase if the violation continues more than 30 days after FDA notifies the responsible person of the violation. The penalties double for the second 30-day period, and continue to double for subsequent 30-day periods, up to $1 million per period and $10 million per proceeding."[6]

The FDA also has the authority to use mechanisms to enforce manufacturers to ensure third parties (physicians, pharmacists, distributors) "take reasonable steps" to monitor and evaluate REMS implementation.[7] However, the FDA does not have any authority to enforce REMS requirements for third parties. But, a third party's ability to prescribe and dispense certain medications, even some that have been on the market for years, could be contingent upon compliance with REMS requirements. And, those parties that fail to comply with REMS requirements are subject to misbranding violations and civil liability. For example, if a pharmacy fails to dispense a medication guide, that may lead to a misbranding violation. What's more, if the patient doesn't receive a medication guide and is injured by the drug, the pharmacy could be held liable in a lawsuit.[8]

The abuse of prescription medications is what led to the passage of the Food and Drug Administration Amendments Act (FDAAA), which took effect March 25, 2008.

Which Drugs Require REMS?

At a time when more and more prescription drug overdoses are being reported, the number of prescriptions for controlled substances is increasing, and more prescription drugs are ending up in the wrong, unintended hands, the number of drugs required to have REMS is increasing. In general, REMS are required for drugs or biologics with significant toxicity levels and/or demonstrable risk factors.[4] Those that have a potential for abuse, misuse, overdose, addiction or teratogenicity (ability to cause birth defects) are likely to require REMS. And, although the FDA evaluates product on a singular basis, they have been more likely to request a REMS for a product that is within a class of products recognized to have a common risk.[9] Six classes of drugs have been identified as requiring such a REMS for each medication: long-acting opioids, fluoroquinolone

antibiotics, anti-epileptic drugs, tumor necrosis factor (TNF) blocking drugs/inhibitors, botulinum toxins and erythropoiesis-stimulating agents.[5]

The FDAAA mandates that the FDA consider certain elements to determine which drugs need REMS. This includes considerations in initial drug product approval, estimated patient population size, seriousness of disease or condition, expected benefit of the drug, expected or actual duration of treatment, seriousness of any known or potential adverse events, whether the drug is a new molecular entity, considerations after drug product approval, availability of new safety information, and new evidence that REMS requirements are needed to ensure that the benefits of a drug outweigh its risks. Among those 160-plus drugs with FDA-approved REMS are some "deemed drugs" that in the past were the subject of risk minimization action plans, known as RiskMAPs, that have now been "grandfathered" in as REMS-approved.[8]

While the FDA has not been granted authority to require a class-wide REMS program, there is debate about whether one should be established. At issue is whether one REMS for an entire class of drugs versus a single REMS for each product in the class will still provide the same safeguards, despite the fact that many of the REMS in a drug class are redundant. At the center of this debate are extended release opioid analgesics, which contain fentanyl, hydromorphone, oxycodone, oxymorphone, methadone or morphine. In 2009, the FDA asked for comments about the proposed class-wide REMS for extended-release opioids, and after more than 2,000 responses, it had extended the comment period until October 2010. An FDA advisory meeting will be held this spring to make a final ruling, which could serve as a precedent for other class-wide REMS.[8]

REMS Problems and Possible Solutions

Many in the healthcare industry believe there are problems with the current REMS process, but most do think it's necessary, and they do offer some possible solutions. The main concerns are what it takes to get a drug through the regulatory process, patient access to a drug, the time and financial investment required, and the effect on product sales.

The complexity in creating a REMS program can place a potential burden on the healthcare system, especially if a class-wide REMS system is established. For instance, Gerard Maher, chief operating officer of REMS Group, Princeton, N.J., a research-based consultancy and training institute that helps clients develop REMS for their products, believes "it would overwhelm the healthcare delivery system if each manufacturer in a drug class had their own REMS." At issue is how fairly the burden of developing, implementing, managing and assessing a REMS program can be distributed among each manufacturer in a drug class. For instance, smaller branded and generic organizations may not have the financial resources to develop and implement a REMS. That, then, may keep some important drugs or cheaper drugs off the market.[10] Marc Boutin, executive vice president and chief operating officer of the National Health Council, agrees: "The reality is we are still not getting new treatments to market as quickly as the patient community would like or need."[11]

The FDAAA grants FDA the authority to impose penalties on manufacturers that do not comply with REMS requirements.

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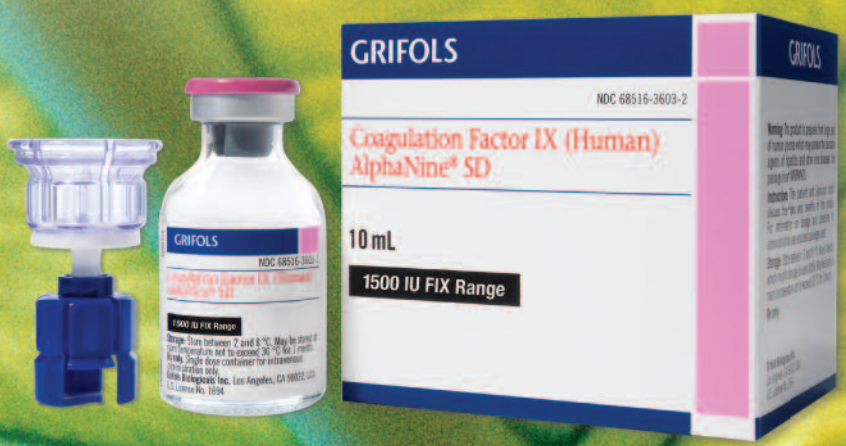

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Some of the more complicated strategies of REMS programs have made it more difficult for physicians to prescribe drugs off-label, which occurs more than 100 million times a year, with at least 20 percent of all prescriptions written off-label. According to Gregory Conko, a senior fellow at the Competitive Enterprises Institute, Washington, D.C., and Henry Miller, a physician and fellow at Stanford University's Hoover Institute and a former FDA official, "The term 'elements to assure safe use' sounds benign enough, but regulators' demands can be so drastically restrictive as to constitute a new, distinct and limited, or conditional, class of approvals — one that makes off-label prescribing much more cumbersome and difficult."[12]

While the FDA has not been granted authority to require a class-wide REMS program, there is debate about whether one should be established.

Kathryn Keller, PharmD, CPE, who is on the board of directors at the American Chronic Pain Association, believes that the stricter the program is, the more burdensome it may be to prescribe. "For at least one of the newly approved, rapid-onset opioids, the fentanyl buccal film, the REMS has presented a significant impediment to access due to its complex requirements and limited sources," she says. However, that may be due to unfamiliarity with the process. "If you look at some of the established REMS programs for non-opioids, with multiple-step programs requiring a patient registry and input of laboratory test results, for example, there was an initial drop in the use of the drug, followed by a return to usual usage as clinicians and patients became familiar with the requirements and understood their purpose," Keller adds.[11]

Patient access also may be affected by the financial and time investment required to execute the additional safe use features of the programs. Gerald Aronoff, MD, DABPM, FAADEP, medical director of Carolina Pain Associates, Charlotte, N.C., says that physicians have only a certain amount of time each visit in which they must write prescriptions and evaluate patients, so they're likely to opt for prescriptions that don't include a rigorous REMS program. He suggests better access to and development of databases of patient prescription information, as well as further research into developing abuse-deterrent opioid drugs.[11]

Maher says he also is worried about "the potential effect on product sales. REMS is adding greater uncertainty to the drug approval process and is also an issue any time safety information is released on a marketed product."[11]

What Now?

Something has to be done to combat the illicit use of legal prescription drugs. The question is: Are REMS working? Many of the concerns raised have to do with complex REMS requirements, meaning all three elements of a REMS program must be in place for the product to be prescribed. But, most FDA-approved REMS drugs require only one of those elements, the medication guide.

The need for a REMS program is clearly warranted, and in the end, the program needs to be a result of a shared solution. Which is why the FDA is working with all parties involved to find a manageable solution. ❖

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

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New Transparency Reporting Guidelines Affecting Physicians

The healthcare reform laws include new strict reporting guidelines for the medical industry, and physicians need to ensure that what is reported is correct to protect their practice.

By Jennifer Kester

Although healthcare reform continues to be hotly debated on Capitol Hill, doctors already have to deal with one topic of the reforms from the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act: transparency in reporting. Responding to concerns about manufacturers' gifts to doctors, these two laws aim to force manufacturers to disclose what typically had been grants of medical supplies and pharmaceuticals

to a public that may see such gifts as a conflict of interest.

An extensive amount of data now has to be reported, and there's a distinct possibility that some of it will be incorrect. And, while the legal responsibility for these disclosures remains with the manufacturer, it will be necessary for doctors to ensure that the information reported by the manufacturer is correct. Also, since this is the first time the government is attempting such a program, there may be complications.

This process isn't entirely new for physicians. Even before these transparency laws were enacted, the American Medical Association (AMA) has had in effect its own board-approved legislative principles on gifts to physicians that encourage doctors to take an active role in the process. According to the AMA, "Ultimately, it is the responsibility of individual physicians to minimize conflicts of interest that may be at odds with the best interest of patients and to access the necessary information to inform medical recommendations."

What Must Be Reported

The manufacturer will be required to report the physician's name and address, the value of payment or gift given (cash or cash equivalent; in-kind items or services; stocks, a stock option, ownership interest or return on investment) and the date the gift was provided. Additionally, the manufacturer must disclose a description of the nature of the gift, such as whether it is for consulting fees, compensation for services other than consulting, honoraria, entertainment, food, travel, education, research, charitable contribution, royalty or license, current or prospective ownership or investment interest, compensation for serving as a speaker or faculty for a continuing medical education program, or a grant. If the gift is related to marketing, education or research specific to a drug, device or a biological or medical supply, the name of that product must be reported as well. All of this information must be reported by Sept. 13, 2013 (and on June 30 each year thereafter), and it must be made available to the public online.

When it comes to product research or development of a new medical technology, a new application of existing technology, or a new drug, device or biological or medical supply for clinical investigations, the information should be made available either after the U.S. Food and Drug Administration approves the drug or item, or four calendar years after the date that the payment was made.

Drug samples also now fall under the reporting requirements. For years, drug manufacturers have been required to collect information about drug samples that they distributed, since many consumers fear that the procurement of samples by doctors influences which prescriptions they are filling for patients. But, this internal information will now be turned over to the federal government to be part of a searchable online database. The identity and quantity of drug samples requested and distributed by doctors seeking the samples must be disclosed starting April 1, 2012.

An extensive amount of data now has to be reported, and there's a distinct possibility that some of it will be incorrect.

Beginning March 31, 2013, manufacturers and group-purchasing organizations will be forced to reveal all physicians (or an immediate family member of the doctors) who have any ownership or investment interest in the company.

However, this doesn't include publicly traded securities or mutual funds. Plus, they must disclose the amount invested by each physician, the value and terms of each ownership or investment interest, and any payment or transfer of value provided to a doctor (or entity or individual who is designated on behalf of the physician) holding such ownership or investment interest.

These laws have been enacted by the government, but still it is not clear what the information-intensive reporting process will look like.

Hospitals also have to disclose any physicians who are owners or investors, as well as the nature and extent of all of their interests. Hospital facilities must implement procedures for physician owners and investors to disclose their interests to patients referred to the hospital. In addition, the hospitals must divulge that they are partially owned or invested in by doctors, either on their websites or by taking out a public advertisement. As a side note, if the hospital does not have a doctor on the premises during all hours of operation, it must tell patients of the limited physician availability prior to admitting them for treatment.

One transparency law that went into effect this past January directly pertains to physicians: Doctors who refer a patient for in-office radiology or imaging services must divulge that there are other nearby providers the patient can use instead. But it's not sufficient to just inform the patient that he or she can receive these services from another provider; doctors have to inform them in writing and list providers who offer the same services in the area in which the patient resides.

One hazy area is the conflict these new federal laws may have with state laws. Although the new federal transparency provisions trump the state laws starting January 1, 2012, the healthcare industry isn't completely exempt from adhering to applicable state reporting laws. If a state's laws go beyond the federal provisions, then those state reporting requirements must still be adhered to. For example, if the state requires someone other than a manufacturer or a physician to do the reporting, that still will be required. And, the state may allow disclosure to a federal, state or local governmental organization for public health surveillance, investigation or other purpose to ensure public health is protected.

What Is Excluded

Of course, there are some exclusions to the new federal reporting guidelines. Any gift under $10 doesn't have to be reported, as long as the total amount during a year given to that doctor does not exceed $100. Since this amount is so small, this basically means that everything will have to be reported. The cap can easily be surpassed by one gratis meal.

Product samples for patients that aren't for sale and educational materials that directly benefit patients, like brochures, also do not have to be reported. Another exception is a device that is loaned for a trial period, as long as the trial period does not exceed 90 days. Any items or services covered under a contractual warranty, including the replacement of a medical device, needn't be reported, since those are not providing anything new of value to doctors. Anything of value that has to do with a civil or criminal action or an administrative proceeding also is exempt. Discounts and in-kind items used for charity care are other exceptions, such as services for Doctors Without Borders or similar organizations, do not fall under these guidelines. And, as previously mentioned, any dividend from an ownership or investment in a publicly traded security or mutual fund does not need to be reported.

The Process

These laws have been enacted by the government, but still it is not clear what the information-intensive reporting process will look like. While there are financial penalties that are meant to keep the manufacturers honest in disclosing their gift-giving practices, there isn't any readily available oversight to ensure that all the information is correct, which means that physicians should be sure to monitor the reporting on their own. When in doubt about a gift from a manufacturer, physicians should look to the AMA's principles for guidance on the matter: "Any gifts accepted by physicians individually should primarily entail a benefit to patients and should not be of substantial value." That means textbooks, modest meals and other gifts are acceptable if they serve an educational function, but cash is not appropriate. An even simpler way to think about it: Don't accept any gifts that you wouldn't want your patients to know about. ❖

JENNIFER KESTER *is a San Diego-based writer and editor specializing in health and lifestyle issues.*

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

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

The ACIP recommendation for annual influenza vaccination now includes all persons aged 6 months and older.[4] FLUVIRIN is indicated for persons 4 years of age and older.

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Indication

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

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

Please see reverse for Important Safety Information.

NOVARTIS VACCINES

Influenza Virus Vaccine Fluvirin®

Important Safety Information

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

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

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

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

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

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NOVARTIS VACCINES

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FLUVIRIN® *(Influenza Virus Vaccine)*

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

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

1 INDICATIONS AND USAGE

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

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

4 CONTRAINDICATIONS

4.1 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

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

5.2 Altered Immunocompetence

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

5.3 Preventing and Managing Allergic Reactions

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

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

5.4 Limitations of Vaccine Effectiveness

Vaccination with FLUVIRIN® may not protect all individuals.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

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

6.2 Clinical Trial Experience

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

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

Adult and Geriatric Subjects

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

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

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

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

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

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

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

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

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

(continued)

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

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

Results reported to the nearest whole percent
-not reported

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

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

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

(continued)

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

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

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

Adults (18 to 64 years of age)

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

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

Geriatric Subjects (65 years of age and older)

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

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

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

Clinical Trial Experience in Pediatric Subjects

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

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

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

6.3 Postmarketing Experience

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

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

6.4 Other Adverse Reactions Associated with Influenza Vaccination

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

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

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

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

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

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

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

7.2 Concurrent Use with Immunosuppressive Therapies

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

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

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An affiliate of: Novartis Vaccines and Diagnostics, Inc.,
350 Massachusetts Avenue, Cambridge, MA 02139 USA
1-800-244-7668

Myths and Facts: Skin Cancer

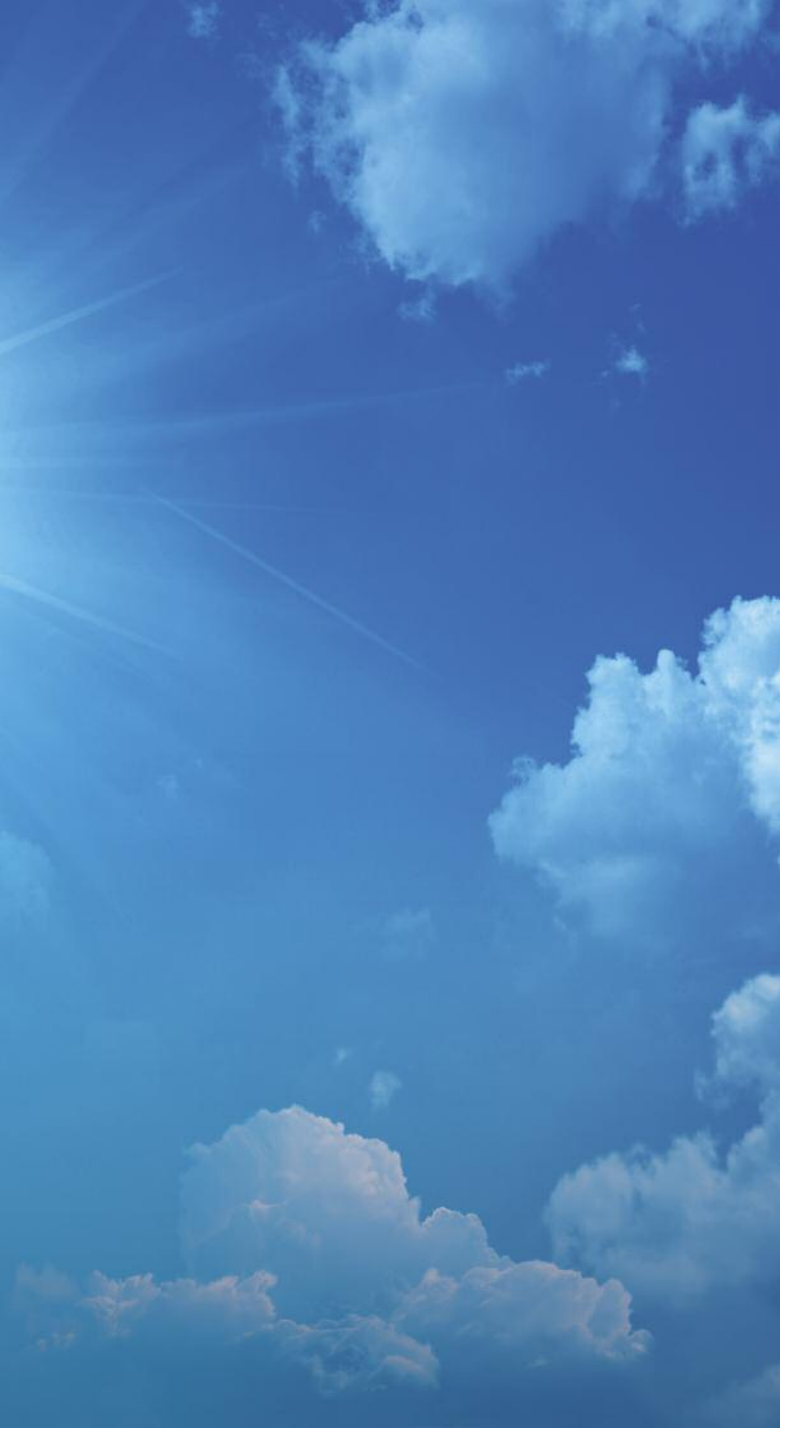
The rising prevalence of skin cancer indicates many people don't understand the risks of sun exposure and how they can protect themselves from this oftentimes deadly disease.

By Ronale Tucker Rhodes, MS

More than one million people in the U.S. are diagnosed each year with cancer. And, while the overall rate of cancer diagnoses has been declining since 1999, this is not true for skin cancer. Instead, skin cancer diagnoses continue to rise each year.[1]

Skin cancer is the 10th most common type of cancer in the U.S. It is divided into two classes: non-melanoma (basal cell and squamous cell carcinomas) and melanoma. Non-melanoma skin cancers are more common, with about 80 percent of all diagnosed skin cancer cases basal cell carcinomas and approximately 16 percent squamous cell carcinomas. Melanoma accounts for only 4 percent of diagnosed cases, but it is the deadliest form of skin cancer.[2] Between 1975 and 2006,[1] the number of melanoma cases increased, and in 2010 alone, there was predicted to be an estimated number of 68,130 new cases.[3]

Why do the rates of skin cancer continue to rise? Likely because of how widely misunderstood it is. But, separating fact from fiction can go a long way toward helping people prevent this oftentimes deadly disease.



Separating Myth from Fact

Myth: Skin cancer is not as serious as other forms of cancer, and is rarely fatal.

Fact: Skin cancer is very serious. There are approximately 11,790 deaths due to skin cancer each year, 8,700 of which are due to melanoma. The overall five-year survival rate for melanoma is 91 percent. As with all other cancers, the earlier the cancer is detected, the more likely one will survive it. For localized melanoma, the five-year survival rate is 98 percent; survival rates for regional and distant stage diseases are 62 percent and 15 percent, respectively. Fortunately, about 84 percent of melanomas are diagnosed at a localized stage.[3]

Myth: Skin cancer is easy to detect.

Fact: It's easy to miss or mistake skin cancer. Melanoma can occur anywhere, including the legs, arms, back, neck, palms of the hands and soles of the feet, so it's important to regularly perform a skin exam.

Even when an exam is performed, it's common for melanoma to be mistaken for moles. But, melanoma has some distinguishing characteristics that can be identified using the ABCD rules: A for asymmetry, B for border, C for color and D for diameter. While common moles are symmetrical and round, melanomas are asymmetrical, so that if a line is drawn through the middle, the halves would not be symmetrical.

Even minimal exposure to the sun causes skin cancer.

Melanomas also are often uneven and have notched edges, whereas moles have even, smooth borders. Moles appear as a single shade of brown, whereas melanomas vary in shades of brown, black and tan, and as they progress, the colors red, blue and white may appear. And, melanomas tend to be larger than moles, which are typically about the size of a pencil eraser.[4]

Myth: People with dark features are not at risk of developing skin cancer.

Fact: People with lighter hair, light-colored eyes and fair skin, as well as those who have numerous moles, are six times more likely to develop melanoma than people with darker features.[5] But, all people are at risk. People with dark skin have additional protection because they have more melanin, which filters UV radiation, but when diagnosed with melanoma, it's typically at an advanced stage.[5]

There also is the mistaken belief that people with a tan are less likely to develop cancer. Tanned skin is just damaged skin, and repeated tanning injures the skin and increases the risk of skin cancer.[6]

Myth: Skin cancer is caused only by prolonged exposure to the sun.

Fact: It is true that excessive sun exposure increases the risk of skin cancer. But, even minimal exposure to the sun causes skin cancer. On a cloudy day, 85 percent of ultraviolet (UV) rays can still penetrate, leaving people equally at risk in the car, walking the dog or letting their children out to play at any time of the year.[6] Even so, the American Academy of Dermatology advises individuals to avoid the sun when its rays are the strongest, between 10 a.m. and 4 p.m.[7]

In a recent study, scientists found that an immune protein actually exacerbates cancer due to sun exposure. Because of the rising rates of melanoma, researchers at George Washington University Medical Center in Washington, D.C., have been examining the link between UV rays and melanoma for more than a decade. In their study, they found that UVB rays cause white blood cells, called macrophages, to migrate higher in the skin of mice and release an immune protein, interferon-y. But, instead of protecting the body like most interferon proteins do, interferon-y allows tumors to grow by preventing the body's natural immune response.[8]

Myth: People need some exposure to the sun to ensure they get enough vitamin D.

Fact: Actually, normal vitamin D levels are primarily maintained through a normal diet, rather than through exposure to sunlight. According to the National Institutes of Health, "Despite the importance of the sun for vitamin D synthesis, it is prudent to limit exposure of skin to sunlight."[9]

Many dermatologists agree. "As a dermatologist who treats the ravages of skin cancer on a daily basis, it is appalling to me that anyone in good conscience could make the claim that intentional sun exposure — for any length of time — is beneficial," says Darrell S. Rigel, MD, clinical professor at the New York University Medical Center in New York. "Until there is science that tells us otherwise, it is imperative that people protect themselves from the sun. Anyone concerned about not getting enough vitamin D should either take a multivitamin or drink a few glasses of vitamin D-fortified milk every day. Given the fact that the U.S. Department of Health and Human Services has declared UV radiation as a known carcinogen, exposing oneself to it for the sake of vitamin D is not the answer."[7]

Myth: Using sunscreen, especially those with high SPF ratings, will prevent skin cancer.

Fact: Sunscreen is not a panacea for preventing skin cancer, but it should be used to reduce risk. And, sunscreen is recommended only as one component of a multipronged sun safety strategy, which also includes wearing protective clothing, limiting sun exposure and avoiding the sun during peak hours. Unfortunately, according to a 2009 survey of 1,000 adults, almost one-third of all Americans don't use sunscreen at all, and 69 percent report using it only occasionally. What's worse are the misconceptions about sunscreen that reduce its effectiveness, even when it is used.[10]

Sunscreen is not a panacea for preventing skin cancer, but it should be used to reduce risk.

SPF, which stands for sun protection factor, is a number that indicates how long it will take for UVB rays to redden skin when using a sunscreen product, compared to how long the skin would take to redden without the product. The higher the SPF, the longer skin can be sun-exposed before burning.[11] But many people believe that once sunscreen is applied, they are protected. Sunscreen should be applied at least every two hours, especially when swimming or sweating, even if the sunscreen is labeled "water-resistant." In addition, it should be applied 15 to 30 minutes prior to going outdoors to allow it time to absorb into the skin. And, after a year, sunscreen loses some of its effectiveness, and it is completely ineffective after three years.[10]

There also is a problem with how sunscreen is labeled and rated. In the U.S., a sunscreen's effectiveness is only measured by SPF, which indicates how much protection it provides against UVB rays. UVB rays, which are short-wave radiation with wavelengths of 290 to 320 nanometers, were long considered the main wavelengths behind skin cancer. However, more recent research shows that UVA rays, long-wave radiation of 320 to 400 nanometers, are the predominant cause of premature skin aging and also a significant cause of skin cancer. While UVA rays don't burn the skin, they invade the skin more deeply than UVB rays, possibly producing even more damage.

Many sunscreens in the U.S. provide UVA defense, but the U.S. has no criteria for determining or labeling a sunscreen's level of UVA protection (whereas outside of the U.S., particularly in Europe, there is such criteria). So, the Food and Drug Administration (FDA) is considering several labeling changes: 1) a one- to four-star rating system would be used to gauge UVA protection, with one star the lowest and four the highest.

Products without a star would be marked "No UVA protection." 2) Sunscreen packaging must include a warning that sunscreen is just one part of a comprehensive sun protection program, along with instructions to reapply every two hours, limit sun exposure and wear protective clothing. 3) Whereas now SPF numbers are as high as 100, they would be limited to 50+. An SPF of 15 filters out 93 percent of UVB, SPF 30 filters out 97 percent and SPF 50 filters out 98 percent. Numbers over 50 offer negligible increases in protection. 4) The term "sun protection factor" would be changed to "sunburn protection factor." 5) The terms "waterproof" and "sunblock" would be disallowed, as no product is impervious to water or able to fully block the sun's rays. Sunscreen that retains its SPF after 40 or 80 minutes of immersion in water would be labeled "water resistant" or "very water resistant," respectively. The FDA had announced that it would rule on these proposals by October 2010, but as of this writing, no ruling has been made.[11]

One last misconception about sunscreen pertains to self-tanners. Self-tanners only stain the skin's top layer a bronze hue. In fact, a German study showed that self-tanners increase sun damage, especially after exposure to sun an hour or so after applying tanner. This is because the skin may produce 180 percent more free radicals (unstable molecules that damage cells, potentially leading to skin cancer) than it would have had the product not been used.[1]

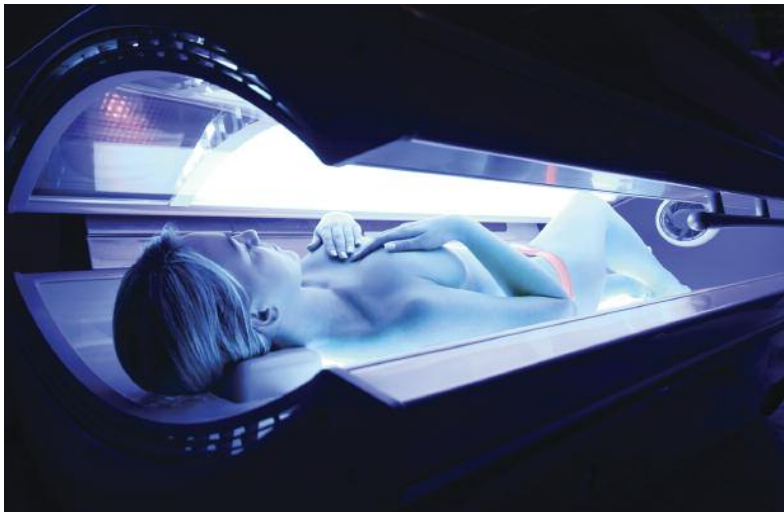
Myth: Indoor tanning beds don't cause skin cancer.

Fact: Twenty minutes of exposure in a tanning bed is roughly equivalent to four hours in the sun.[5] Unfortunately, while teen indoor tanning has decreased since 2005, recent usage by girls remains high, with more than 10 percent of all girls ages 14 to 17 and 16 percent of non-Hispanic white girls of the same age using an indoor tanning device in 2008.[1]

Twenty minutes of exposure in a tanning bed is roughly equivalent to four hours in the sun.

Myth: People who have had prior prolonged sun exposure or sunburns don't need to worry about getting skin cancer if they take care of themselves later.

Fact: It can take up to 20 or more years for skin cancer to develop. It was originally reported by the Skin Cancer Foundation that most people receive about 80 percent of their lifetime sun exposure before age 18. But, recently, the Skin Cancer Foundation revealed that 47 percent occurs between ages 19 and 40. By protecting against sun exposure now, it's possible to lessen the effects of past exposure. A study in the *New England Journal of Medicine* showed that people who used sunscreen daily saw a reduction in the number of new precancerous sun spots and a slowing development of preexisting ones.[12]



Dispelling the Myths Now

The days of lathering with oil and lying in the sun for hours upon hours are history. But, that hasn't stopped the incidence of skin cancer from rising. Individuals need to be factually informed about what they can do to prevent this deadly disease before it is too late for them or a loved one. ❖

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

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A Fake and a Fraud

A research scandal raises new questions about the safety of synthetic colloids in place of human albumin.

by KEITH BERMAN, MPH, MBA

THE EMERGING NEWS of shocking ethics violations and fabricated clinical research by a prominent clinical expert in fluid resuscitation therapy reminds us that no profession is untarnished by the corrupting influences of greed or the drive for self-aggrandizement.

Professor Joachim Boldt is — or rather was — regarded as a world authority on fluid management in surgery and a prolific clinical researcher with more than 200 peer-reviewed articles to his name. Over more than a decade at his academic hospital across the Rhine from Mannheim, Germany, Dr. Boldt has churned out dozens of clinical studies evaluating the functionality and safety of a class of synthetic colloids broadly called hydroxyethyl starch (HES) or "hetastarch." HES products directly compete with commercial preparations of purified 5% human albumin, the natural water-retaining colloid that comprises roughly two-thirds of our circulating plasma protein content.

In recent years, Dr. Boldt has been an increasingly vociferous advocate of substituting certain synthetic colloids — waxy long-stranded substances derived from corn called HES — for human albumin in surgical fluid volume resuscitation. In numerous commentaries published in leading anesthesia and critical care journals, Dr. Boldt passionately espoused the safety and benefits of newer hetastarch products, while questioning the clinical relevance, value and even the safety of human albumin.

Fraud on the Banks of the Rhine

Then last Oct. 28, the editor of the journal *Anesthesia & Analgesia* delivered a bombshell.[1] Several concerned readers had written to express doubts about a December 2009 study it published titled "Cardiopulmonary Bypass Priming Using a High Dose of a Balanced Hydroxyethyl Starch Versus an Albumin-Based Priming Strategy."[2] The variability in results of a particular cytokine assay was too low to be believed, they argued. So too was the reported variability in blood gas findings in this trial, which randomized 50 patients to receive either an electrolyte-balanced "low-molecular-weight" HES product or 5% human albumin and saline in their cardiopulmonary bypass (CPB) pumps prior to open-heart surgery. The lead author of this study was Dr. Joachim Boldt.

In his Oct. 28 letter, the editor of Anesthesia & Analgesia retracted Dr. Boldt's faked 2009 HES-versus-albumin study.

Joachim Boldt, MD

Inquiries by the journal led to an investigation by the Rheinland State Medical Board (LÄK), which determined that Dr. Boldt never secured Institutional Review Board (IRB) approval for this trial conducted at his hospital. There were no records documenting subject informed consent. There was no evidence of a randomization process or a follow-up questionnaire as described in the study.

Reported findings from Dr. Boldt's study perhaps should also have aroused the suspicions of anyone familiar with the major physiological functions of

human albumin (see the table, Functions of Human Serum Albumin) or numerous earlier studies clearly associating the use of earlier-generation HES products with impaired hemostasis and excessive blood loss in typically hypothermic, hemodiluted and heparinized patients undergoing cardiac surgery.[3,4] "High-volume priming of the CPB circuit with a modern balanced HES solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal tubular integrity compared with an albumin-based priming," Dr. Boldt and his five co-authors concluded. "Coagulation including platelet function was better preserved with high-dose balanced HES CPB priming compared with albumin-based CPB priming."

Except their study didn't actually happen. It now appears that Dr. Boldt made up the results. According to the head of the perfusion team at his hospital, Klinikum Ludwigshafen, no albumin has been used as a priming solution there since 1999. No albumin has been delivered to the cardiac operating rooms "for many years," the hospital's pharmacy told LÄK investigators. No original patient data or laboratory findings could be found to support the findings in the study.

In his Oct. 28 letter, the editor of *Anesthesia & Analgesia* retracted Dr. Boldt's faked 2009 HES-versus-albumin study. Published editorials in that journal now conclude that the findings were "fabricated." Dr. Boldt has not denied this. Late last year, he was dismissed from his institution, where he had served as chief of anesthesiology and intensive care.

Meanwhile, the LÄK is continuing its investigation, which it acknowledges could take many months or even years to complete. In late February, the LÄK established that IRB approval could not be verified for 89 of 101 examined studies, including 22 between 1999 and 2009 that were published in *Anesthesia & Analgesia*. All 89 studies have been declared "unethical"

Klinikum Ludwigshafen

and retracted by a total of 16 U.S. and international journals. An investigating committee commissioned by Klinikum Ludwigshafen is now painstakingly comparing published findings in each of those 89 studies to actual patient and laboratory records to determine whether the reported results were authentic or were faked by Dr. Boldt as well.

What We Don't Know About Voluven

Whether real or fabricated, the contributions of Dr. Boldt and his hospital account for a substantial share of all HES clinical research literature published during the last decade. Most of his studies presumptively evaluated newer low-molecular-weight HES products, which have a shorter circulating half-life but also have a less-pronounced adverse impact on platelet function and coagulation factor levels that can impair hemostasis.[5]

One of those products is Voluven (6% HES 130/0.4 in 0.9% sodium chloride), manufactured by Fresenius Kabi and launched in the U.S. in September 2008. The prescribing information for Voluven specifies that up to 50 mL/kg — 3.5 liters for the average adult — may be administered per day. This dosing limit far exceeds the recommended daily maximum of 1,500 mL specified for HEXTEND (6% HES in Lactated Electrolyte Injection) or HESPAN (6% HES in 0.9% sodium chloride).

Like other HES products, Voluven is heavily promoted as a less-costly alternative to human albumin. This corn starch-derived synthetic colloid is indeed marginally less costly than albumin. But before substituting Voluven for 5% albumin, physicians and pharmacists arguably should expect to see results from clinically relevant head-to-head comparisons of the two products in sufficiently large randomized studies to

Functions of Human Serum Albumin

- Accounts for about 75 percent of intravascular colloid oncotic pressure; binds and holds water
- Transports many drugs; affects circulating half-life of many drugs
- Acts as a heme-binding protein, reducing its pro-oxidant properties
- Exerts systemic and circulatory anti-inflammatory actions
- Binds and transports numerous endogenous and exogenous compounds, variously facilitating physiologic function, detoxification and antioxidant protection:
  - bilirubin
  - thyroid and fat-soluble hormones
  - metal ions
  - free fatty acids
  - amino acids

Source: Quinlan, GJ, Martin, GS, and Evans, TW. Albumin: Biochemical properties and therapeutic potential. *Hepatology*, 2005;41(6):1211-19.

detect important differences in the risk of infrequent but potentially serious adverse events. In the setting of major surgery, variation in presenting problems, patient age and underlying comorbidities can make connecting the use of a new agent and adverse outcomes extremely difficult if not impossible without a large randomized trial to overwhelm the effects of these various "confounders."

In promotional material posted online by Voluven's U.S. distributor, Dr. Boldt was the senior author on four of the eight clinical studies that evaluated the product in adults.[6] Just two studies in adults compared Voluven with 5% albumin. Both were conducted — if they were conducted at all — by Dr. Boldt and colleagues. In a very implausible coincidence, each of these two studies enrolled 50 subjects, randomized 25:25 to each treatment arm, exactly the same number and randomization as the faked 2009 cardiac surgery trial retracted by *Anesthesia & Analgesia*.

It thus appears that no credible head-to-head clinical trial has been performed in adult subjects to try to ascertain the safety of Voluven in relation to albumin. But there is a second problem that applies equally to other HES products that include HEXTEND, HESPAN and generic equivalents: No clinical trial pitting any of them against albumin has been large enough to identify important but relatively infrequent adverse outcomes. While drug regulators routinely require large studies of new drugs for such common conditions as diabetes, hypertension and prostate disorders, no such standard is applied for novel resuscitative fluids or drugs used in vast numbers of surgeries in often seriously ill patients.

The Human Price of Underpowered Trials

The price paid for this laxity in clinical testing standards has been steep. Consider aprotinin, an antifibrinolytic agent approved in 1993 and marketed for 14 years as Trasylol for use in limiting bleeding in cardiac surgery. This drug was administered to untold thousands of patients until a large Canadian trial finally confirmed suspicions that Trasylol increased the risk of kidney failure, heart attack, stroke and death. The drug was finally withdrawn from the market in 2007.

It thus appears that no credible head-to-head clinical trial has been performed in adult subjects to try to ascertain the safety of Voluven in relation to albumin.

Closer to home, HES products gained favor in the 1990s as a less-costly alternative to human albumin for CPB pump priming and perioperative volume resuscitation. At an FDA advisory panel meeting in 2002, a colleague and I shared published evidence from several single-center "lookback" studies showing that rates of serious bleeding and transfusion requirements jumped when surgeons switched from albumin to HES. Shortly thereafter, the U.S. Food and Drug Administration (FDA) amended HES product labeling to include a warning against "use as a cardiac bypass pump prime, while the patient is on cardiopulmonary bypass, or in the immediate period after the pump has been discontinued."

In both of these unfortunate examples, the requirement of a large adequately powered randomized trial for approval would have exposed infrequent serious risks that individual surgeons and anesthesiologists could not hope to identify in their own very limited and heterogeneous patient pools. And, of course, it would have averted needless harm and lost lives.

Moving Past the Boldt Scandal

The absence of large randomized trials comparing newer HES products like Voluven against albumin has obligated both regulators and clinicians to rely on reviews or meta-analyses of small independent and manufacturer-sponsored trials. Recognizing the grim prospect that an unusually prolific researcher may have fabricated most if not all of his HES-related clinical study findings, investigators in Australia and Canada are now conducting new meta-analyses of the available HES clinical literature that purposely exclude all studies published by Dr. Boldt.

The Canadian group, led by Dr. Ryan Zarychanski, a critical care specialist at the University of Manitoba, recently published a systematic review and meta-analysis assessing renal outcomes and mortality in patients admitted to the intensive care unit (ICU) who received HES solutions or alternative resuscitative fluids, including albumin.[7] This 2009 review of 22 randomized controlled trials in the online journal *Open Medicine* determined that patients given HES were significantly more likely to have acute kidney injury (odds ratio 1.90, 95% confidence interval, 1.22-2.96). In the subset of trials that included patients with severe sepsis or septic shock and in "high-quality" and multicenter trials, there was a trend toward increased risk of death associated with HES.

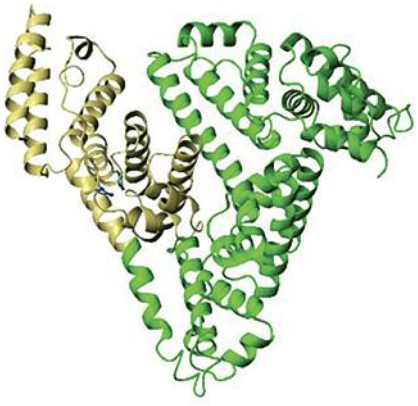
Shortly after Dr. Boldt's HES-versus-albumin CPB study was retracted by *Anesthesia & Analgesia* last October, the authors of this meta-analysis posted the following statement preceding their report:

"ATTENTION: The analysis and conclusions of this article are being revised by the authors. This is due to the journal *Anesthesia & Analgesia*'s retraction of a paper by Dr. Joachim Boldt, an author in seven of the studies analyzed in this review. As such, the editors of *Open Medicine* recommend interpreting this review with extreme caution until Zarychanski et al. publish a new analysis and interpretation."

This group plans to revise its analysis after ongoing investigations resolve questions about the integrity of those seven Boldt studies, among the roughly 200 under scrutiny.

What these meta-analyses cannot fully answer is whether Voluven or other HES products are as safe as human albumin in a broad cross-section of surgical patients, including patients with serious comorbidities such as sepsis or renal insufficiency. To get those answers, one must conduct a large randomized clinical trial. No such trial is currently in progress, but the same consortium of Australian and New Zealand researchers is currently doing the next best thing: a massive 7,000-subject trial comparing 90-day mortality in ICU patients randomized to receive Voluven or saline fluid resuscitation.[8]

This same team in 2004 published the landmark Saline Versus Albumin Fluid Evaluation (SAFE) study of similar size, which documented similar 28-day mortality with administration of albumin and saline in a heterogeneous ICU population. Interestingly, in a cohort of more than 1,200 severe sepsis patients, there was a strong trend toward reduced mortality in those who received human albumin instead of saline (relative risk 0.87, 95% CI, 0.74-1.02).[9]



X-ray crystallographic structure of human serum albumin

Next Up for Voluven: Post-Marketing Studies

The FDA approved Voluven in 2007 on the condition that the manufacturer committed to conducting two post-marketing studies:

1. A multiple-dose, randomized controlled trial in subjects with severe sepsis with or without renal dysfunction; and

2. A comparison of Voluven and 5% human albumin in open-heart surgery in 2- to 12-year-old pediatric patients.

Hindsight is always 20/20, but given the absence of any large-scale trials evaluating the safety of Voluven against any other resuscitative fluid, perhaps those trials would better have been completed before approving the product without restrictions or warnings about risks in cardiac surgery or a status of clinical sepsis.

With serious (if not grave) concerns about the validity of several key Voluven trials performed at a single center by a now-disgraced researcher, there is now an obvious urgency to complete these trials and answer the unanswered safety questions.

Voluven and its class of low-molecular-weight HES products are novel by virtue of their lesser effect on the coagulation system than older-generation HES solutions. It specifically restores colloid oncotic pressure where saline or other crystalloids do not.

But in patients who have lost a lot of blood, and particularly in those with serious comorbidities or compromised physiological reserve, I suggest the jury is still out on whether this one-trick colloid is a worthy peer of a humble molecule that is anything but novel.

That would be human albumin, the most abundant and pharmacologically versatile protein in the human bloodstream, and the most perfect colloid nature could create. ❖

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

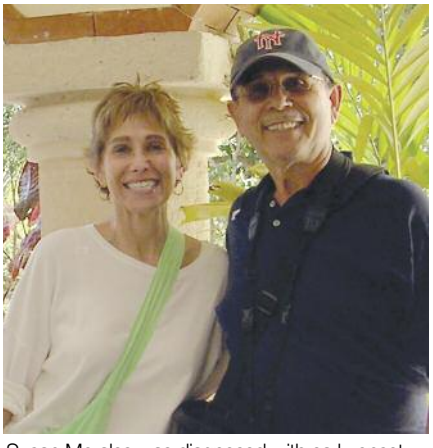
Holding Out Hope

If you think Alzheimer's disease affects only the very elderly, think again. Early-onset Alzheimer's can strike in midlife, with devastating consequences. But hope is on the horizon.

by TRUDIE MITSCHANG

IT'S A COMMON joke at cocktail parties. Someone in their early 50s laments a sudden tendency to misplace their eyeglasses or keys, and inevitably someone chimes in: "It must be Alzheimer's!" People chuckle because no one that young really believes this memory-ravaging disease is an imminent threat. After all, Alzheimer's is an "old person's disease." Or is it?

With her shiny auburn hair, lithe dancer's figure and radiant smile, Susan Morales does not fit the stereotypical image of an Alzheimer's patient. Susan was 51 years old and at the top of her game as a regional director for a national insurance company when friends and colleagues began noticing a change in her behavior and personality. A high-energy, detail-oriented high-achiever, Susan had begun absent-mindedly repeating herself and seemed to struggle to gather her thoughts before speaking. It was her boss who eventually suggested she see a doctor. "Looking back, I was definitely in denial," says Susan. "I'm a UCLA graduate and a registered nurse, so I could tell something was off. But nothing could have prepared me for the final diagnosis."



Susan Morales was diagnosed with early-onset Alzheimer's at age 51.

According to the Mayo Foundation for Medical Education and Research, early-onset Alzheimer's disease only accounts for 5 to 10 percent of all cases of Alzheimer's disease.

Susan underwent a battery of tests that included an MRI, PET scan, CT scan, lumbar puncture, psychological evaluations and blood work. Then in 2005, at the age of 55, Susan was diagnosed with early-onset Alzheimer's.

Understanding Early-Onset Alzheimer's

Early-onset Alzheimer's, also called familial Alzheimer's disease, is a rare, inherited form of Alzheimer's that affects individuals younger than 65 years of age. According to the Mayo Foundation for Medical Education and Research, early-onset Alzheimer's disease accounts for only 5 to 10 percent of all cases of Alzheimer's disease. Those who contract the disease early in life almost always have a family history of Alzheimer's. If even one parent has early-onset Alzheimer's, offspring have a 50 percent chance of inheriting the disease. If both parents have the disease, children will eventually suffer from it too. But statistics always have exceptions; in Susan's case, there is no family history of Alzheimer's at all. She suffers from a variant form of the disease for which there is still little scientific data.

The symptoms of Alzheimer's are the same for both late- and early-onset, as are treatment options. Many people take medication and are encouraged to adopt healthy lifestyle choices to slow the progression of the disease. Although some experts believe that early-onset Alzheimer's progresses at a faster rate, evidence supporting this theory remains inconclusive. It may be that in younger people the decline in mental functioning is more noticeable and, therefore, appears to be occurring at a

faster rate. But each case of Alzheimer's is as unique as the individual battling the disease.

"What we've learned is that if you've met one Alzheimer's patient, you've really only met one Alzheimer's patient," explains Serge Morales, Susan's husband. "Everyone reacts differently to medication and treatment. In Susan's case, we've been fortunate, because most people meeting her for the first time have no idea she suffers from this disease."

for patients and caregivers.

Over the last 15 years, scientists have made enormous strides in understanding how Alzheimer's disease affects the brain. Current FDA-approved drugs temporarily improve the symptoms of the disease; they do not stop the damage to brain cells that causes the disease to progress. But scientists remain optimistic that in the near future, therapies and treatments that slow or stop the progression of the disease will be available.

Susan's IVIG study at the University of Southern California will evaluate the effectiveness and safety of immune globulin in slowing the progression of Alzheimer's.

Exploring Treatment Options

Alzheimer's is a progressive degenerative disease with no cure. At best, current treatments can slow the worsening of symptoms and improve quality of life

Susan was fortunate because she had access to some of the best medical and research facilities at UCLA Medical Center in Los Angeles. Susan's physician, Mario F. Mendez, MD, PhD, is a behavioral neurologist at the forefront of dementia-related research. "Dr. Mendes immediately put me on Aricept and Namenda, two FDA-approved medications for Alzheimer's symptoms," Susan says. "I also participated in a clinical trial for RI (rage inhibitor), and I am currently in the early stages of a clinical trial for intravenous immune globulin (IVIG)."

Susan's IVIG study at the University of Southern California will evaluate the effectiveness and safety of immune globulin in slowing the progression of Alzheimer's. Because it contains anti-amyloid antibodies, IVIG is being studied as a treatment for Alzheimer's disease. Researchers believe that IVIG may act on some of the underlying causes of Alzheimer's instead of just on its symptoms, which would be a huge breakthrough for patients like Susan.

Susan has made more than 35 trips to raise funds and awareness about Alzheimer's disease.

Discovering New Priorities

Being diagnosed with Alzheimer's in your 50s immediately alters your plans and priorities. Shortly after her diagnosis, Susan took an early retirement and relinquished her driver's license, making her dependent on Serge for tasks large and small. The transition to this level of dependence has not been easy, but Susan and Serge say they have chosen to allow this affliction to bring them closer together, dedicating their free time and

Susan and her husband, Serge, continue to stay active by traveling and attending support groups to connect with other early-onset Alzheimer's patients.

energy to advocacy work. Both have become active in the Southern California chapter of the Alzheimer's Association, speaking at 35-plus fundraising events and making multiple trips to Washington, D.C., to raise awareness and encourage more research funding.

"I didn't want to be the face of early-onset Alzheimer's, but I need to show people that this is a disease that is not just affecting seniors," Susan says. "If I can help raise awareness about this, it's worth the time and effort."

In addition to their advocacy work, Susan and Serge say they have endeavored to stay active, attending and hosting dinner parties, and traveling to Europe and Mexico in recent years. Susan also attends a support group twice monthly where she connects with other early-onset patients. Serge has found it helpful to attend a separate support group for caregivers. "It's important to have a safe place to share your feelings and find out how others are coping," Serge says.

With a degenerative disease like Alzheimer's, the prognosis for the future is unknown, a fact that is unsettling at best. But for patients like Susan, dealing with short-term memory loss has forced her to do what many healthy individuals struggle to accomplish: live in the moment. "I remain optimistic and hopeful," says Susan. "There are so many advances in treatment and that's encouraging. That's why when people ask me how I'm doing, I can honestly say: 'Right now, I'm doing very well.'" ❖

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

Key Facts About Alzheimer's

- In May 2010, Alzheimer's disease became the sixth-leading cause of death, according to the Centers for Disease Control and Prevention.
- Two out of three people diagnosed with cancer will be cured. But many of those same people will age and die of Alzheimer's.
- Currently, 5.3 million people have Alzheimer's and 10.9 million serve as caregivers.
- African-Americans are twice as likely, and Hispanics are 1.5 times more likely than whites to develop the disease.
- One out of eight baby boomers will be diagnosed with Alzheimer's.
- Every 70 seconds, someone in America develops Alzheimer's. By midcentury, someone will develop the disease every 33 seconds.

Source: 2010 Alzheimer's Key Facts and Figures Report: www.alz.org/alzheimers_disease_facts_and_figures.asp

Deliver comprehensive protection with **HyperRAB® S/D** and **RabAvert®** Rabies Vaccine.

According to CDC guidelines, you need both a rabies immune globulin, such as HyperRAB S/D, and a vaccine, such as RabAvert Rabies Vaccine, to provide proper care to previously unvaccinated patients potentially exposed to the rabies virus.[1]

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IMPORTANT SAFETY INFORMATION for HyperRAB® S/D

Rabies vaccine and HyperRAB S/D should be given to all persons suspected of exposure to rabies with one exception: persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine.

HyperRAB S/D (Rabies Immune Globulin [Human]) should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

The attending physician who wishes to administer HyperRAB S/D to persons with isolated immunoglobulin A (IgA) deficiency must weigh the benefits of immunization against the potential risks of hypersensitivity reactions. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

Soreness at the site of injection and mild temperature elevations may be observed at times. Sensitization to repeated injections has occurred occasionally in immunoglobulin-deficient patients. Angioneurotic edema, skin rash, nephrotic syndrome, and anaphylactic shock have rarely been reported after intramuscular injection so that a causal relationship between immunoglobulin and these reactions is not clear.

Administration of live virus vaccines (e.g., MMR) should be deferred for approximately 3 months after rabies immune globulin (human) administration.

HyperRAB S/D 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.

IMPORTANT SAFETY INFORMATION for RabAvert®

RabAvert (rabies vaccine) is indicated for preexposure vaccination, in both primary series and booster dose, and for postexposure prophylaxis against rabies in all age groups.

Anaphylaxis, encephalitis including death, meningitis, neuroparalytic events such as encephalitis, transient paralysis, Guillain-Barré syndrome, myelitis, and retrobulbar neuritis; and multiple sclerosis have been reported to be temporally associated with the use of RabAvert.

The most commonly occurring adverse reactions are injection site reactions, such as injection site erythema, induration and pain; flu-like symptoms; arthralgia; dizziness; lymphadenopathy; nausea; and rash. History of anaphylaxis to the vaccine or any of the vaccine components constitutes a contraindication to preexposure vaccination with this vaccine. In the case of postexposure prophylaxis, if an alternative product is not available, vaccination should proceed with caution and close observation. A patient's risk of acquiring rabies must be carefully considered before discontinuing vaccination.

Please see adjacent pages for brief summaries of HyperRAB S/D and RabAvert Rabies Vaccine full Prescribing Information.

Reference: 1. Manning SE, Rupprecht CE, Fishbein D, et al; Centers for Disease Control and Prevention. Human rabies prevention—US, 2008: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 2008;57(RR-3):1-38.

 August 2010 HY92-0810 NVDRAB052

Hyper**RAB**™ S/D

Rabies Immune Globulin (Human) Solvent/Detergent Treated

BRIEF SUMMARY
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INDICATIONS AND USAGE
Rabies vaccine and Rabies Immune Globulin (Human) — Hyper**RAB**™ S/D should be given to all persons suspected of exposure to rabies with one exception: persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine. Hyper**RAB** S/D should be administered as promptly as possible after exposure, but can be administered up to the eighth day after the first dose of vaccine is given.

Recommendations for use of passive and active immunization after exposure to an animal suspected of having rabies have been detailed by the U.S. Public Health Service Advisory Committee on Immunization Practices (ACIP).

Every exposure to possible rabies infection must be individually evaluated. The following factors should be considered before specific antirabies treatment is initiated:

1. Species of Biting Animal

Carnivorous wild animals (especially skunks, foxes, coyotes, raccoons, and bobcats) and bats are the animals most commonly infected with rabies and have caused most of the indigenous cases of human rabies in the United States since 1960. Unless the animal is tested and shown not to be rabid, postexposure prophylaxis should be initiated upon bite or nonbite exposure to these animals (see item 3 below). If treatment has been initiated and subsequent testing in a competent laboratory shows the exposing animal is not rabid, treatment can be discontinued.

In the United States, the likelihood that a domestic dog or cat is infected with rabies varies from region to region; hence, the need for postexposure prophylaxis also varies. However, in most of Asia and all of Africa and Latin America, the dog remains the major source of human exposure; exposures to dogs in such countries represent a special threat. Travelers to those countries should be aware that >50% of the rabies cases among humans in the United States result from exposure to dogs outside the United States.

Rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are rarely found to be infected with rabies and have not been known to cause human rabies in the United States. However, from 1971 through 1988, woodchucks accounted for 70% of the 179 cases of rabies among rodents reported to CDC. In these cases, the state or local health department should be consulted before a decision is made to initiate postexposure antirabies prophylaxis.

2. Circumstances of Biting Incident

An unprovoked attack is more likely to mean that the animal is rabid. (Bites during attempts to feed or handle an apparently healthy animal may generally be regarded as provoked.)

3. Type of Exposure

Rabies is transmitted only when the virus is introduced into open cuts or wounds in skin or mucous membranes. If there has been no exposure (as described in this section), postexposure treatment is not necessary. Thus, the likelihood that rabies infection will result from exposure to a rabid animal varies with the nature and extent of the exposure. Two categories of exposure should be considered:

Bite: any penetration of the skin by teeth. Bites to the face and hands carry the highest risk, but the site of the bite should not influence the decision to begin treatment.

Bat-associated strains of rabies can be transmitted to humans either directly through a bat's bite or indirectly through the bite of an animal previously infected by a bat. Because some bat bites may be less severe, and can go completely undetected, unlike bites inflicted by larger animals, especially mammalian carnivores, rabies postexposure treatment should be considered for any physical contact with bats when bite or mucous membrane contact cannot be excluded.

Nonbite: scratches, abrasions, open wounds or mucous membranes contaminated with saliva or any potentially infectious material, such as brain tissue, from a rabid animal constitute nonbite exposures. If the material containing the virus is dry, the virus can be considered noninfectious. Casual contact, such as petting a rabid animal and contact with the blood, urine, or feces (e.g., guano) of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis. Instances of airborne rabies have been reported rarely. Adherence to respiratory precautions will minimize the risk of airborne exposure.

The only documented cases of rabies from human-to-human transmission have occurred in patients who received corneas transplanted from persons who died of rabies undiagnosed at the time of death. Stringent guidelines for acceptance of donor corneas have reduced this risk.

Bite and nonbite exposures from humans with rabies theoretically could transmit rabies, although no cases of rabies acquired this way have been documented.

4. Vaccination Status of Biting Animal

A properly immunized animal has only a minimal chance of developing rabies and transmitting the virus.

5. Presence of Rabies in Region

If adequate laboratory and field records indicate that there is no rabies infection in a domestic species within a given region, local health officials are justified in considering this in making recommendations on antirabies treatment following a bite by that particular species. Such officials should be consulted for current interpretations.

Rabies Postexposure Prophylaxis
The following recommendations are only a guide. In applying them, take into account the animal species involved, the circumstances of the bite or other exposure, the vaccination status of the animal, and presence of rabies in the region. Local or state public health officials should be consulted if questions arise about the need for rabies prophylaxis.

Local Treatment of Wounds: Immediate and thorough washing of all bite wounds and scratches with soap and water is perhaps the most effective measure for preventing rabies. In experimental animals, simple local wound cleansing has been shown to reduce markedly the likelihood of rabies.

Tetanus prophylaxis and measures to control bacterial infection should be given as indicated.

Active Immunization: Active immunization should be initiated as soon as possible after exposure (within 24 hours). Many dosage schedules have been evaluated for the currently available rabies vaccines and their respective manufacturers' literature should be consulted.

Passive Immunization: A combination of active and passive immunization (vaccine and immune globulin) is considered the acceptable postexposure prophylaxis except for those persons who have been previously immunized with rabies vaccine and who have documented adequate rabies antibody titer. These individuals should receive vaccine only. For passive immunization, Rabies Immune Globulin (Human) is preferred over antirabies serum, equine. It is recommended both for treatment of all bites by animals suspected of having rabies and for nonbite exposure inflicted by animals suspected of being rabid. Rabies Immune Globulin (Human) should be used in conjunction with rabies vaccine and can be administered through the seventh day after the first dose of vaccine is given. Beyond the seventh day, Rabies Immune Globulin (Human) is not indicated since an antibody response to cell culture vaccine is presumed to have occurred.

Rabies Postexposure Prophylaxis Guide

Animal species	Condition of animal at time of exposure/attack	Treatment of exposed person [1]
Dog and cat	Healthy and available for 10 days of observation	None, unless animal develops rabies [2]
	Rabid or suspected rabid	RIGH [3] and HDCV
	Unknown (escaped)	Consult public health officials
Skunk, bat, fox, coyote, raccoon, bobcat, and other carnivores; woodchuck	Regard as rabid unless animal proven negative by laboratory tests [4]	RIGH [3] and HDCV
Livestock, rodents, and lagomorphs (rabbits and hares)	Consider individually. Local and state public health officials should be consulted on questions about the need for rabies prophylaxis. In most geographical areas bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares almost never require antirabies postexposure prophylaxis.	

[1] ALL POSTEXPOSURE PROPHYLAXIS SHOULD BEGIN WITH IMMEDIATE THOROUGH CLEANSING OF THE WOUND (IF ONE CAN BE DETECTED) WITH SOAP AND WATER. If antirabies treatment is indicated, both Rabies Immune Globulin (Human) [RIGH] and human diploid cell rabies vaccine (HDCV) should be given as soon as possible, REGARDLESS of the interval from exposure.

[2] During the usual holding period of 10 days, begin postexposure prophylaxis at first sign of rabies in a dog or cat that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.

[3] If RIGH is not available, use antirabies serum, equine (ARS). Do not use more than the recommended dosage.

[4] The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.

CONTRAINDICATIONS
None known.

WARNINGS
Rabies Immune Globulin (Human) — HyperRAB**™ S/D 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. 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 the patient.

Hyper**RAB** S/D should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

The attending physician who wishes to administer Hyper**RAB** S/D to persons with isolated immunoglobulin A (IgA) deficiency must weigh the benefits of immunization against the potential risks of hypersensitivity reactions. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

PRECAUTIONS
General
Hyper**RAB** S/D should **not** be administered intravenously because of the potential for serious reactions. Although systemic reactions to immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactoid symptoms.

Drug Interactions
Repeated doses of Hyper**RAB** S/D should not be administered once vaccine treatment has been initiated as this could prevent the full expression of active immunity expected from the rabies vaccine.

Other antibodies in the Hyper**RAB** S/D preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within 3 months after Hyper**RAB** S/D administration.

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

Pediatric Use
Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS
Soreness at the site of injection and mild temperature elevations may be observed at times. Sensitization to repeated injections has occurred occasionally in immunoglobulin-deficient patients. Angioneurotic edema, skin rash, nephrotic syndrome, and anaphylactic shock have rarely been reported after intramuscular injection, so that a causal relationship between immunoglobulin and these reactions is not clear.

CAUTION
℞ only

U.S. federal law prohibits dispensing without prescription.

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

08938814-BS

RabAvert®
Rabies Vaccine
only

Rabies Vaccine for Human Use

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

Indications and Usage

RabAvert is indicated for preexposure vaccination, in both primary series and booster dose, and for postexposure prophylaxis against rabies in all age groups. *See **Indications and Usage** and **Dosage and Administration** sections in the full prescribing information.*

Contraindications

In view of the almost invariably fatal outcome of rabies, there is no contraindication to postexposure prophylaxis, including pregnancy. *Hypersensitivity:* History of anaphylaxis to the vaccine or any of the vaccine components constitutes a contraindication to preexposure vaccination with this vaccine. In the case of postexposure prophylaxis, if an alternative product is not available, the patient should be vaccinated with caution with the necessary medical equipment and emergency supplies available and observed carefully after vaccination. A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination. Advice and assistance on the management of serious adverse reactions for persons receiving rabies vaccines may be sought from the state health department or CDC.

Warnings

Anaphylaxis, encephalitis including death, meningitis, neuroparalytic events such as encephalitis, transient paralysis, Guillain-Barré Syndrome, myelitis, and retrobulbar neuritis; and multiple sclerosis have been reported to be temporally associated with the use of RabAvert. *See **Precautions** and **Adverse Events** sections.* A patient's risk of developing rabies must be carefully considered, however, before deciding to discontinue immunization. RABAVERT MUST NOT BE USED SUBCUTANEOUSLY OR INTRADERMALLY. RabAvert must be injected intramuscularly. For adults, the deltoid area is the preferred site of immunization; for small children and infants, administration into the anterolateral zone of the thigh is preferred. The use of the gluteal region should be avoided, since administration in this area may result in lower neutralizing antibody titers. DO NOT INJECT INTRAVASCULARLY. Unintentional intravascular injection may result in systemic reactions, including shock. Immediate measures include catecholamines, volume replacement, high doses of corticosteroids, and oxygen. Development of active immunity after vaccination may be impaired in immunecompromised individuals. Please refer to **Drug Interactions**, under **Precautions**. This product contains albumin, a derivative of human blood. It is present in RabAvert at concentrations of less than 0.3 mg/dose. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeld-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Precautions

General: Care is to be taken by the health care provider for the safe and effective use of the product. The health care provider should also question the patient, parent or guardian about 1) the current health status of the vaccinee; and 2) reactions to a previous dose of RabAvert, or a similar product. Preexposure vaccination should be postponed in the case of sick and convalescent persons, and those considered to be in the incubation stage of an infectious disease. A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis and other infectious agents from person to person. Needles should not be recapped and should be properly disposed of. As with any rabies vaccine, vaccination with RabAvert may not protect 100% of susceptible individuals. *Hypersensitivity:* At present there is no evidence that persons are at increased risk if they have egg hypersensitivities that are not anaphylactic or anaphylactoid in nature. Although there is no safety data regarding the use of RabAvert in patients with egg allergies, experience with other vaccines derived from primary cultures of chick embryo fibroblasts demonstrates that documented egg hypersensitivity does not necessarily predict an increased likelihood of adverse reactions. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reaction to vaccines produced in primary cultures of chick embryo fibroblasts. Since reconstituted RabAvert contains processed bovine gelatin and trace amounts of chicken protein, neomycin, chlortetracycline and amphotericin B, the possibility of allergic reactions in individuals hypersensitive to these substances should be considered when administering the vaccine. Epinephrine injection (1:1000) must be immediately available should anaphylactic or other allergic reactions occur. When a person with a history of hypersensitivity must be given RabAvert, antihistamines may be given; epinephrine (1:1000), volume replacement, corticosteroids and oxygen should be readily available to counteract anaphylactic reactions. *Drug Interactions:* Radiation therapy, antimalarials, corticosteroids, other immunosuppressive agents and immunosuppressive illnesses can interfere with the development of active immunity after vaccination, and may diminish the protective efficacy of the vaccine. Preexposure vaccination should be administered to such persons with the awareness that the immune response may be inadequate. Immunosuppressive agents should not be administered during postexposure therapy unless essential for the treatment of other conditions. When rabies postexposure prophylaxis is administered to persons receiving corticosteroids or other immunosuppressive therapy, or who are immunosuppressed, it is important that a serum sample on day 14 (the day of the fourth vaccination) be tested for rabies antibody to ensure that an acceptable antibody response has been induced. HRIG must not be administered at more than the recommended dose, since active immunization to the vaccine may be impaired. No data are available regarding the concurrent administration of RabAvert with other vaccines. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* Long-term studies with RabAvert have not been conducted to assess the potential for carcinogenesis, mutagenesis, or impairment of fertility. *Use in Pregnancy:* Pregnancy Category C. Animal reproductive studies have not been conducted with RabAvert. It is also not known whether RabAvert can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RabAvert should be given to a pregnant woman only if clearly needed. The ACIP has issued recommendations for use of rabies vaccine in pregnant women. *Use in Nursing Mothers:* It is not known whether RabAvert is excreted in animal or human milk, but many drugs are excreted in human milk. Although there are no data, because of the potential consequences of inadequately treated rabies exposure, nursing is not considered a contraindication to postexposure prophylaxis. If the risk of exposure to rabies is substantial, preexposure vaccination might also be indicated during nursing. *Pediatric Use:* Children and infants receive the same dose of 1 mL, given IM, as do adults. Only limited data on the safety and efficacy of RabAvert in the pediatric age group are available. However, in three studies some preexposure and postexposure experience has been gained *(see also **Clinical Studies in Clinical Pharmacology** section in the full prescribing information). Geriatric Use:* Clinical studies of RabAvert did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Adverse Reactions

In very rare cases, neurological and neuroparalytical events have been reported in temporal association with administration of RabAvert *(see also **Warnings** section).* These include cases of hypersensitivity *(see **Contraindications, Warnings, and Precautions** sections).* The most commonly occurring adverse reactions are injection site reactions, such as injection site erythema, induration and pain; flu-like symptoms, such as asthenia, fatigue, fever, headache, myalgia and malaise; arthralgia, dizziness, lymphadenopathy, nausea, and rash. A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination. Advice and assistance on the management of serious adverse reactions for persons receiving rabies vaccines may be sought from the state health department or CDC *(see also **Contraindications** section).* Local reactions such as induration, swelling and reddening have been reported more often than systemic reactions. In a comparative trial in normal volunteers, Dreesen *et al.* described their experience with RabAvert compared to a HDCV rabies vaccine. Nineteen subjects received RabAvert and 20 received HDCV. The most commonly reported adverse reaction was pain at the injection site, reported in 45% of the HDCV group, and 34% of the RabAvert group. Localized lymphadenopathy was reported in about 15% of each group. The most common systemic reactions were malaise (15% RabAvert group vs. 25% HDCV group), headache (10% RabAvert group vs. 20% HDCV group), and dizziness (15% RabAvert group vs. 10% HDCV group). In a recent study in the USA, 83 subjects received RabAvert and 82 received HDCV. Again, the most common adverse reaction was pain at the injection site in 80% in the HDCV group and 84% in the RabAvert group. The most common systemic reactions were headache (52% RabAvert group vs. 45% HDCV group), myalgia (53% RabAvert group vs. 38% HDCV group) and malaise (20% RabAvert group vs. 17% HDCV group). None of the adverse events were serious, almost all adverse events were of mild or moderate intensity. Statistically significant differences between vaccination groups were not found. Both vaccines were generally well tolerated. Uncommonly observed adverse events include temperatures above 38°C (100°F), swollen lymph nodes, pain in limbs and gastrointestinal complaints. In rare cases, patients have experienced severe headache, fatigue, circulatory reactions, sweating, chills, monoarthritis and allergic reactions; transient paresthesias and one case of suspected urticaria pigmentosa have also been reported. *Observed During Clinical Practice (See **Warnings** and **Precautions**)* The following adverse reactions have been identified during postapproval use of RabAvert. Because these reactions are reported voluntarily from a population of uncertain size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to RabAvert, or a combination of these factors: Allergic: Anaphylaxis, Type III hypersensitivity-like reactions, bronchospasm, urticaria, pruritus, edema; CNS: Neuroparalysis, encephalitis, meningitis, transient paralysis, Guillain-Barré Syndrome, myelitis, retrobulbar neuritis, multiple sclerosis, vertigo, visual disturbance; Cardiac: Palpitations, hot flush; Local: Extensive limb swelling. The use of corticosteroids to treat life-threatening neuroparalytic reactions may inhibit the development of immunity to rabies *(see **Precautions**, Drug Interactions).* Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully managed with anti-inflammatory and antipyretic agents. *Reporting of Adverse Events:* Adverse events should be reported by the health care provider or patient to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Report forms and information about reporting requirements or completion of the form can be obtained from VAERS by calling the toll-free number 1-800-822-7967. In the USA, such events can be reported to the Professional Services department, Novartis Vaccines and Diagnostics, Inc.: phone: 1-800-244-7668.

Storage

RabAvert should be stored protected from light at 2°C to 8°C (36°F to 46°F). After reconstitution the vaccine is to be used immediately. The vaccine may not be used after the expiration date given on package and container.

Manufactured by:
Novartis Vaccines and Diagnostics GmbH & Co. KG
D-35006 Marburg, Germany
US License No. 1754

Distributed by:
Novartis Vaccines and Diagnostics, Inc.
Emeryville, CA 94608, USA

Rev. 10/06

Relational Leadership: A People-First Approach

"I like to surround myself with great people, give them a definitive, almost palpable vision, then move out of the way and strive to keep up with them!"

by TRUDIE MITSCHANG

FINDING YOUR LIFE'S passion in the context of your career is an aspiration for many, although few are fortunate enough to make a living doing what they love. For Chris Ground, chief operating officer at FFF Enterprises Inc., in Temecula, Calif., the man, the mission and the vision have clearly merged. For more than 13 years, Ground has played an instrumental role in helping FFF, the nation's largest distributor of critical care biopharmaceuticals, achieve a flawless safety track record. While many factors have contributed to this stellar achievement, Ground sums it up pretty simply: "We never lose sight of the fact that the product moving through our secure channel is for a patient. Safety must be, and therefore is, at the center of everything we do."

Practicing What He Preaches

As a leader, Ground is known for practicing what he preaches: "When you move into a leadership role, people begin to pay attention to what you say and how you conduct business. It's really important to lead by example, something I endeavor to do in my personal and professional life." Ground maintains an open-door policy that encourages collaboration and fosters the team environment he values. Despite a recent promotion, he stresses that leadership is relational rather than positional.

For more than 13 years, Ground has played an instrumental role in helping FFF, the nation's largest distributor of critical care biopharmaceuticals, achieve a flawless safety track record.

In a culture that is more collegial than corporate, this relational style lends itself to a high-performing, committed team that, as he says, takes their work, but not themselves, seriously. "I like to surround myself with great people, give them a definitive, almost palpable vision, then move out of the way and strive to keep up with them," says Ground. "Everyone wants to be a part of something greater than themselves, and if you can get people to embrace the vision, they will want to get there as a team. When you have a team like that, there's no stopping you."

Making Patient Safety His No. 1 Priority

Ground's career includes 18 years on the manufacturer's side of the business where he developed a somewhat cynical view of product distribution channels. The shady tactics he witnessed firsthand left him with little desire to ever "switch teams." That is, until destiny intervened in the form of a meeting with Patrick M. Schmidt, chief executive officer of FFF, that convinced him that there was one distributor focused on creating a secure supply chain and putting patient safety first.

"At the time, the distribution chain was considered unseemly to say the least," recalls Ground. "It was common for distributors, especially during times of short supply, to practice price gouging and other unsafe handling practices. When Patrick started talking to me about tracking lots right down to the patient, and securing the supply chain, he immediately got my attention. He was describing a company that could potentially change the way business was done, in a way that would ultimately benefit patients. I wanted to be a part of that."

Since joining FFF in 1998, Ground has helped the company grow from $178 million in annual revenue to more than $1 billion. He also has played a pivotal role in making FFF the leading distributor of albumin, intravenous immune globulin (IVIG) and flu vaccine in the country. In his current role as chief operating officer, Ground oversees the various business units and innovative programs for the company.

Ground's initial reason for joining FFF, his passion for patient safety, has been instrumental in bringing the company into a leadership position on the subject of pharmaceutical supply chain safety. "It's a source of great pride that the mission that resonated so strongly with me when first speaking with Patrick has become a reality," says Ground. "We have impacted this industry in a positive way, and I couldn't be more fulfilled." The company has implemented what it calls the 8 Critical Steps to Guaranteed Channel Integrity, an intricate system of safeguards that includes product lot tracking, high-tech storage, handling and shipping guidelines, and a commitment to purchase products only from the manufacturer, and to distribute only to healthcare providers.

Ground's dedication to product and supply chain safety has its roots in a painful personal experience. During the early 1980s, Ground lost a dear friend who contracted AIDS from a tainted blood transfusion. As referenced in the article titled "Good Blood" featured in this issue of *BioSupply Trends Quarterly*, the HIV infection in our nation's blood supply 30 years ago put a spotlight on the need for viral inactivation technologies and more stringent safety and screening steps within the blood/plasma industry.

Ground's dedication to product and supply chain safety has its roots in a painful personal experience.

"That experience added to what had already become a personal passion," says Ground. "Over the years, I've had the privilege of touring many of our manufacturing partners' plants and have observed the pride they take in the purity of their product, as well as their stringent safety guidelines. Understanding the role the supply chain plays in product safety is extremely important, and everybody along the way has to take some responsibility and accountability. At FFF, we take our role very seriously."

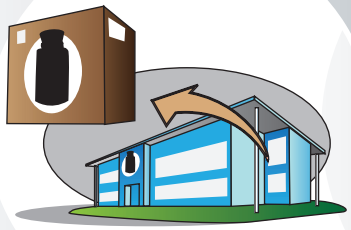
Looking to the Future

As he looks to FFF's future, Ground is excited about expanding the company's industry relationships and sphere of influence. "We have embraced a much more comprehensive relationship with all the stakeholders in healthcare, including patients, providers and payers," he explains. "We believe our industry is in a pivotal time of change, and as a result, we are looking at various models that will still meet our end goal: to get the critical-care products we distribute from the manufacturer to the patient in the safest and most efficient way possible. It takes a team that goes far beyond our corporate walls, and I feel blessed to work with such great partners — from the manufacturers and payers, to the patients and advocacy groups — that all share this worthwhile vision." ❖

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

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

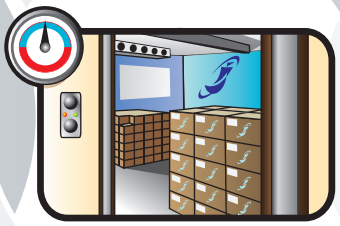
BRINGING TRUST TO



1

PURCHASING

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



2

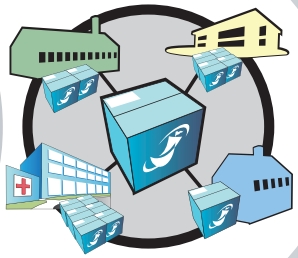
STORAGE

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

3

SPECIALTY PACKAGING

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



4

INTERACTIVE ALLOCATION

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

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

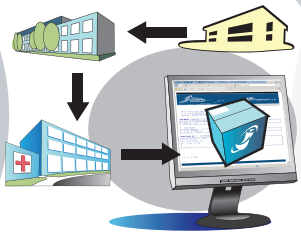
THE MARKETPLACE

5

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

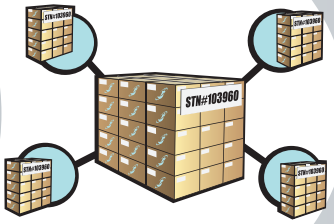
6

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



7

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



8

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

The 8 Critical Steps to Guaranteed Channel Integrity™

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

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

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

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BioProducts

Temperature-Sensitive Packaging Solution

The Orcatherm packaging solution is designed for the transport and intermediate storage of temperature-sensitive materials, such as medicines, biomaterials and pharmaceutical and technical instruments. It is a heavy-duty, ruggedized passive temperature-controlled shipping system, which is completely reusable and is designed with encapsulated vacuum insulated panels that produce up to seven times the insulating effects as the same thickness of other materials. Orcatherm also incorporates next-generation bio-based phase change technology that provides enhanced thermal performance and decreases the total weight and volumetric weight of the shipping system.

Intelsius, (317) 873-8100, www.intelsius.com

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Adaptive TCR's new immunoSEQ profiling service and immunoSEQ Analyzer bioinformatics software platform provide researchers and clinicians the ability to profile and monitor the adaptive immune system, as well as contribute to the understanding and development of medical conditions and applications, including cancer immunotherapy, autoimmune disorders, vaccine development and infectious diseases. ImmunoSEQ assays use proprietary chemistry to amplify the rearranged CDR3 regions of T-cell receptor genes responsible for most TCR diversity. Each immunoSEQ assay can generate millions of cell-specific sequences, allowing for a deep characterization of the T-cell repertoire in any sample. To use the assays and analyzer, a DNA sample is provided, and the company does all the lab work and uploads the resulting sequence data to a secure website that is available to the researcher at all times.

Adaptive TCR Corp. (206) 659-0067, www.adaptivetcr.com

The Pain Cushion

L.M.X.4 is a 4 percent lidocaine topical anesthetic cream available without a prescription. It comes in a variety of sizes, including 5 gram, 15 gram and 30 gram tubes, as well as 5-by-5 gram tubes with Tegaderm and 30 gram tubes with Tegaderm for cases where occlusion may be necessary (e.g., pediatrics).

Eloquest Healthcare, (877) 433-7626,
www.eloquesthealthcare.com/products/lmx4.aspx

Secure Medical Record Portal

The MediConnect Secure Provider Upload Portal enables healthcare providers and facilities to upload medical records and other files directly to MediConnect for processing, eliminating the need to send information via secured fax or traditional mail. Clients can submit a record request through MediConnect's RapidRetrieve system (the company's proprietary retrieval and review service) by logging into the site, entering the password provided in the request letter, selecting one or more scanned medical records and uploading them to securely deliver the files. Users can upload more than one file at a time and provide specific notes or instructions with each file prior to uploading them. To ensure safe and HIPAA-compliant transmission of information, all customer transactions on the portal are protected by 128-bit SSL security verified by Entrust.

MediConnect Global Inc., (800) 489-8710, www.mediconnect.net

Dual-Chamber Syringe

A new prefilled dual-chamber syringe for the administration of Xyntha antihemophilic factor (recombinant) plasma/albumin-free is available to hemophilia A patients. Both the Xyntha powder and the diluent are supplied within the syringe, eliminating the transfer step during reconstitution. The syringe contains 3000 IU of Xyntha, the highest dose, in a low 4 mL volume, and other dosages will be available this year.

Pfizer Inc., (212) 733-2323, www.xyntha.com

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BioResearch

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Influenza Vaccination Reduces Pneumonia Severity During Flu Season

In 2,368 German patients evaluated during the influenza season, community-acquired pneumonia (CAP) was less severe in those who had received influenza vaccination than in those who had not, according to findings from an observational, multicenter cohort study. Severity of CAP on hospital admission was assessed using the CURB score, which includes four criteria: confusion, blood-urea nitrogen level, respiratory rate and blood pressure.

CAP in vaccinated patients was significantly less severe (odds ratio for CURB score ≥1 was 0.76, 95% confidence interval [CI] 0.60-0.98). These patients also experienced significantly better overall survival within the six-month follow-up period (hazard ratio 0.63, 95% CI, 0.45-0.89). As expected, within an off-season cohort of 2,632 patients, there was no significant influence of vaccination status on CAP severity or disease outcome. The investigators concluded that prior influenza vaccination was associated with less-severe clinical course and improved overall long-term survival in patients with CAP during influenza season.

Tessmer, A, Welte, T, Schmidt-Ott, R, et al. Influenza vaccination is associated with reduced severity of community acquired pneumonia. European Respiratory Journal, *Dec. 9, 2010 [Epub ahead of print].*

Prophylactic von Willebrand Factor Therapy Reduces Bleeds in Patients with Severe von Willebrand Disease

Prophylactic von Willebrand factor (VWF) replacement therapy significantly reduces the median number of bleeding episodes in 39 subjects severely affected with von Willebrand disease (VWD), according to new findings from the VWD International Prophylaxis Study. Patients experienced a median of 12 (range two to 54) bleeding episodes per year prior to initiation of prophylaxis, versus an annualized median of four (range zero to 24) bleeding episodes during prophylaxis with VWF ($p<0.0001$). Annualized bleeding rates were lower during prophylaxis for all primary indications, reaching statistical significance ($p<0.05$) for joint bleeding, epistaxis and gastrointestinal bleeding.

In this European and North American patient cohort, type 3 VWD accounted for the largest share of patients (24/39), followed by type 2A (7/39), type 2B (5/39), type 1 (2/39) and type 2M (1/39). The median age at onset of prophylaxis therapy was 29 years (range 2 to 76). The usual number of infusions of VWF during prophylaxis was two to three times per week, with a median usual dose of 45 units of VWF:RCo per kilogram per infusion. A prospective clinical trial organized by the von Willebrand Disease Prophylaxis Network is now under way; its objectives are to develop guidelines for dosing and to address issues of cost-effectiveness and quality of life.

Berntorp, E, Abshire, TC, and Federici, AB. IVIG blocks complement deposition mediated by anti-GM1 antibodies in multifocal motor neuropathy. 52nd Annual Meeting of the American Society of Hematology (Orlando, Fla.), Dec. 6, 2010, Abstract #236.

Human Albumin Reduces Endothelial Dysfunction; Improves Survival in Mouse Model of Sepsis

Infusion of human serum albumin formulated at a 4% concentration significantly improved survival time in Swiss mice injected with lipopolysaccharide (LPS) endotoxin, while 20% human albumin and normal saline provided no protective benefit, according to French investigators. The 4% human albumin, but not the other solutions, also reduced LPS-induced renal dysfunction.

Separately, in human uterine vein endothelial cells exposed to both LPS and tumor necrosis factor-α in the presence or absence of 4% or 20% human albumin, the 4% product activated endothelial nitric oxide synthase and restored LPS-impaired flow-dependent endothelial dilation in mesenteric arteries. The 4% human albumin blunted LPS-tumor necrosis factor-α-induced oxidative and nitrosative stresses in endothelial cells and increased their glutathione levels, while the 20% albumin solution did not.

The investigators concluded that their data confirm a protective effect of 4% human serum albumin treatment measured both by survival in this sepsis model, and by reduced endothelial dysfunction through inhibition of inflammatory and oxidative stress pathways induced by endotoxins. Conversely, much higher concentrations of human albumin were detrimental, suggesting a dose-dependent effect.

Kremer, H, Baron-Menguy, C, Tesse, A, et al. Human serum albumin improves endothelial dysfunction and survival during experimental endotoxemia: Concentration-dependent properties. Critical Care Medicine, *Feb. 17, 2011 [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

Medicare Reimbursement Rates
Rates are effective April 1 through June 30, 2011.

Product	Manufacturer	HCPCS	Hospital Outpatient ASP+5% (per gram)	Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$61.817	$62.406
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$70.764	$71.438
GAMMAGARD LIQUID	Baxter BioScience	J1569	$76.052	$76.776
GAMMAGARD S/D	Baxter BioScience	J1566	$61.817	$62.406
GAMMAPLEX	Bio Products Laboratory Limited	J1599	$74.586*	$74.586
GAMUNEX-C	Talecris Biotherapeutics	J1561	$74.512	$75.222
PRIVIGEN	CSL Behring	J1459	$69.567	$70.230

*ASP + 6% (Medicare pass-through drug)

Calculate your reimbursement online at www.FFFenterprises.com.

REFERENCE TABLES

IG Reference Table

Product	Size	Manufacturer	Indications
CARIMUNE NF (Lyophilized)	3 g, 6 g, 12 g	CSL Behring	PIDD, ITP
FLEBOGAMMA 5% & 10% DIF (Liquid)	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols	PIDD
GAMMAGARD LIQUID (10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Baxter BioScience	PIDD
GAMMAGARD S/D (Lyophilized, 5% or 10%)	2.5 g, 5 g, 10 g	Baxter BioScience	PIDD, ITP, CLL, KD
GAMMAPLEX (Liquid, 5%)	5 g, 10 g	Bio Products Laboratory Limited	PIDD
GAMUNEX-C (Liquid, 10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Talecris Biotherapeutics	PIDD, ITP, CIDP
GAMUNEX-C (Liquid, 10%, SCIG)	1 g, 2.5 g, 5 g, 10 g, 20 g	Talecris Biotherapeutics	PIDD
HIZENTRA (Liquid, 20%, SCIG)	5 mL, 10 mL, 20 mL	CSL Behring	PIDD
PRIVIGEN (Liquid, 10%)	5 g, 10 g, 20 g	CSL Behring	PIDD, ITP
VIVAGLOBIN (Liquid, 16%, SCIG)	3 mL, 10 mL, 20 mL	CSL Behring	PIDD

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

2011-2012 Influenza Vaccine

Administration Codes: G0008 (Medicare plans) 90471 (non-Medicare plans)
Diagnosis Code: V04.81

Product	Size	When Administered to Indicated Age Group	Code
FLUZONE Pediatric	0.25 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90655
AFLURIA	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
FLUZONE	0.5 mL single-dose vial		
FLUZONE	0.5 mL prefilled syringe		
FLUVIRIN	0.5 mL prefilled syringe		
FLUZONE	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to individuals 3 years and older, for intramuscular use	Q2035
FLUVIRIN	5 mL multi-dose vial		Q2037
FLUZONE	5 mL multi-dose vial		Q2038
FLUZONE High-Dose	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use	90662
FLUMIST	0.2 mL nasal spray	Influenza virus vaccine, live, for intranasal use, when administered to individuals 2-49 years of age	90660

GAMUNEX®-C

Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®-C safely and effectively. See full prescribing information for GAMUNEX-C.

GAMUNEX-C, [Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified]

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 occur with immune globulin intravenous (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.**

----------INDICATIONS AND USAGE----------

GAMUNEX-C is an immune globulin injection (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. Have epinephrine 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.
- GAMUNEX-C is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMUNEX-C subcutaneously in patients with ITP.
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may 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 (AMS) has been reported with GAMUNEX-C and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. Monitor patients for hemolysis and hemolytic anemia.
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
- Volume overload
- GAMUNEX-C is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.
- Passive transfer of antibodies may confound serologic testing.

----------ADVERSE REACTIONS----------

- **PI** – The most common adverse reactions (≥5%) with intravenous use of GAMUNEX-C were headache, cough, injection site reaction, nausea, pharyngitis and urticaria. The most common adverse reactions (≥5%) with subcutaneous use of GAMUNEX-C were infusion site reactions, headache, fatigue, arthralgia and pyrexia.
- **ITP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, vomiting, fever, nausea, back pain and rash.
- **CIDP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, fever, chills, hypertension, rash, nausea and asthenia.

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 transiently interfere with the response to live viral vaccines, such as measles, mumps and rubella. Passive transfer of antibodies may confound serologic testing.

----------USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: no human or animal data. Use only if clearly needed.
- Geriatric: In patients over 65 years of age do not exceed the recommended dose, and infuse GAMUNEX-C at the minimum infusion rate practicable.

Talecris BIOTHERAPEUTICS

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

08939771/08939782-BS
Revised: October 2010

The PROOF is everywhere you look

GAMUNEX-C is the IG therapy supported by robust clinical trials

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

Important Safety Information for GAMUNEX-C

Gamunex-C, Immune Globulin Injection (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).

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gamunex-C does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gamunex-C at the minimum concentration available and the minimum infusion rate practicable.

Gamunex-C 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.

Gamunex-C is not approved for subcutaneous use in patients with ITP or CIDP. **Due to the potential risk of hematoma formation, Gamunex-C should not be administered subcutaneously in patients with ITP.**

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

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, coagulation disorders, prolonged periods of immobilization and/or known or suspected hyperviscosity.

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

The high dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Gamunex-C 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.

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

In clinical studies, the most common adverse reactions with Gamunex-C were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria with intravenous use (in PI) and infusion site reactions, headache, fatigue, arthralgia and pyrexia with subcutaneous use (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions in clinical studies 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-C full Prescribing Information.

Evidence based. Patient proven.

gamunex®-C

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

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

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