July 2011

BioSupply Trends

Special Focus: VACCINES

Quarterly

Global Vaccines

Improving Vaccination Rates Around The World

An Ounce of Prevention: The Value of Vaccines

Vaccines: New Diagnoses & Treatment Options

IVIG: Evolution of the Manufacturing Process

Myths & Facts About Antibiotics

New Uses for Therapeutic Plasma Exchange — Page 64

Developed Specifically for the Treatment of von Willebrand Disease

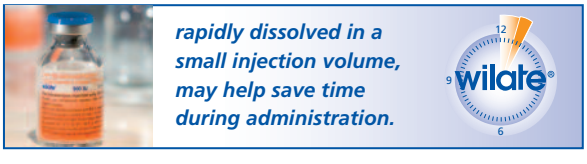
wilate®

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.

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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.

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U.S. License No. 1646

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octapharma

For the safe and optimal use of human proteins

BioSupply Trends Quarterly

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Features

Special Focus: Vaccines

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

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For information about advertising in *BioSupply Trends Quarterly*, you may request a media kit from Cheryl Brooks at (800) 843-7477 x1177, cbrooks@fffenterprises.com.

Vaccines Past, Present and Future

IMAGINE A WORLD without vaccines. For those living in affluent countries today, it is difficult to envision life — or more accurately, the increased illness and death that would be part of life — without this preventive benefit. But, prior to the dawn of bacteriology and to rapid developments in the 1930s of antitoxins and vaccines against infectious diseases, this was the world that existed. Our feature The Value of Vaccines explores the transformative role immunization has played in our world. Yet statistics show that more Americans die each year from vaccine-preventable diseases than from car accidents, breast cancer or AIDS.

While vaccines have proved to be the greatest public health achievement of the 20th century, vaccine complacency could become the greatest public health crisis. Couple our lack of personal experience with the infectious diseases that immunizations have eradicated with misinformation or simply lack of education, and the real epidemic may become non-vaccine compliance. The need for the medical community to educate and advocate on behalf of vaccine awareness, safety and efficacy has never been more urgent.

We have noted a surge of news on this topic, and have included a piece in our BioNews section regarding a survey of healthcare professionals that shows a majority of their office visit time is spent answering concerns about child vaccinations. While many doctors will ask parents to sign a waiver, others simply choose to refer them to another practice — essentially "firing" non-compliant patients. With documentation of once-eradicated diseases beginning to make a comeback, this may not be as rash as it first sounds. According to an article published in January on the Homeland Security Newswire, the 2010 California whooping cough outbreak, which was the worst whooping cough epidemic since 1947, may have been the result of decreases in vaccinations among children.

In this issue, we also take a close look at global access to vaccines. It used to take as long as 20 years for a vaccine that was available in affluent countries to become available in developing countries. That timeline has been significantly compressed, and today it is estimated that increased access to vaccines globally has saved more than 20 million children. With the collaboration of vaccine manufacturers, world partners and individual countries, the hope is that one day vaccines may be introduced simultaneously around the world.

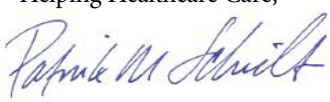
As we traverse from the past to the present, we cannot help but also look forward with our feature Vaccines: A Paradigm Shift. It is exciting to see the broadening role of vaccines beyond prevention, to their use as a diagnostic tool to evaluate immune-deficient and autoimmune diseases, as well as a new treatment option for a host of diseases.

And beyond vaccines, biopharmaceuticals that save and sustain lives deliver their own magic. Our feature IG: The Evolution of the Manufacturing Process explores the modifications in the steps and ingredients of the manufacturing process of immune globulin since the first generation of IVIG was made commercially available in the U.S.

We know that reimbursement is a hot topic in our industry, and we hope you find our Reimbursement FAQs in each issue helpful. I am very pleased to announce our new Reimbursement Unraveled blog that debuted in June. This blog is an interactive forum to provide information, as well as for you to ask questions and share information and experiences on the critical reimbursement issues that impact you and your patients.

We hope you find this issue insightful and helpful to you and your colleagues. ❖

Helping Healthcare Care,



Patrick M. Schmidt, Publisher

BioSupply Trends Quarterly

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

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Healthcare Reform Update

As the struggle over the details of the Affordable Care Act persists, changes continue to be made. The following are the most recent updates as of this writing:

Appeals of insurance denials: The original delay of health insurance denial appeals rules has once again been put off, from July 2011 to January 2012. The rules now on hold include:

• a reduction in the amount of time an insurance company is allowed to review a denial of coverage in urgent cases, from no more than 72 hours to 24 hours;

• a requirement that insurers provide information about the denial and how to appeal in appropriate language for non-English speaking beneficiaries; and

• a requirement that insurers must provide consumers with specific details that would include diagnostic codes used by doctors, hospitals and insurance companies and what treatment isn't covered and why

The reason for the extended grace period, according to the announcement posted on the Labor Department's website, is because the government intends to modify the rules "in the near future." However, what those changes might be has not been disclosed.

Medicaid incentive grants: A federal grant program authorized in the health overhaul law provides states with $100 million to reward Medicaid recipients who make an effort to quit smoking or keep their weight, blood pressure or cholesterol levels in check. The goals of the program are to place more emphasis on the role of preventive health in targeting the underlying causes of chronic disease, as well as to reduce Medicaid costs associated with chronic illnesss, which accounts for more than 75 percent of the $2.5 trillion the U.S. spends on healthcare, according to data from the Department of Health and Human Services.

States have some flexibility about how to design their incentive programs. However, there are federal guidelines. Medicaid enrollees who demonstrate a commitment to improving their health will be eligible to receive financial rewards such as coupons or gift certificates. For instance, those who are overweight or trying to quit smoking might be offered weight-management classes or tobacco-cessation counseling. And, the rewards would be on a tiered basis, from "attempts at participation," to "actual behavior change" and "achievement of health goals."

Bills limit reform funding. Five bills have been approved by the House Energy and Commerce's Health Subcommittee that aim to limit the Department of Health and Human Services (HHS) secretary's spending authority under the health reform law, as well as subject some of the statute's mandatory spending to the annual appropriations process. The bills change a provision that gives the HHS secretary an unlimited amount of funds for state-based exchange grants by canceling unlimited direct appropriation and rescinding any unobligated funds. They also repeal the section of the law that creates a prevention and public health fund and gives the HHS secretary full authority to administer that funding, which totals $17.75 billion from fiscal year 2012 to 2021.

Repeal of 1099 tax reporting provision. President Obama has signed HR4, a bill that repeals a provision that required business and real estate owners to file a 1099 form with the Internal Revenue Service for every vendor to whom they paid more than $600 in a year. The $22 billion cost of the 1099 legislation was offset by requiring some people, if their income level increases during the year, to pay back a portion of the subsidies they receive to join health insurance exchanges.

Temporary healthcare reform waivers exceed 1,000. As of March, the number of healthcare reform waivers granted by the Obama administration was 1,040. These waivers grant a one-year exemption from a new coverage requirement to organizations that cannot meet new annual coverage limits in 2011. According to the HHS, the waivers have typically been granted to so-called "mini-med" plans that offer limited annual coverage — as low as $2,000 — that would fall short of meeting the new annual coverage floor of $750,000 in 2011.

The waivers are meant as a stopgap measure until new state-run insurance exchanges open in 2014, when annual dollar limits will be abolished. Approximately 2.6 million people are covered by the waivers, which represents less than 2 percent of privately insured individuals, according to HHS. ❖

Bill Proposed to Expand Medication Therapy Management

A new law is being proposed that would allow Medicare patients who have a chronic condition to review all their medications in one-on-one sessions with pharmacists, helping them to stick to their drug regimen. Known as medication therapy management, the bill was introduced in March by Sen. Kay Hagan (D-N.C.), along with two original co-sponsors: Reps. Cathy McMorris Rodgers (R-Wash.) and Mike Ross (D-Ark.).

Currently, only about 12.9 percent of seniors in the Medicare prescription drug program are eligible to participate in medication therapy management because they have multiple chronic conditions. The bill would expand that eligibility to people who have only one chronic condition, as well as to dual eligibles enrolled in both Medicare and Medicaid, while requiring prescription drug plan sponsors to reimburse pharmacists and other healthcare providers who provide the service.

A recent analysis by the New England Healthcare Institute, a nonprofit research organization, shows that Americans who don't stay on their drug regimens cost the system as much as $290 billion a year, or 13 percent of total expenditures. ❖

California Affordable Drug Coverage Bill Passes

In May, the California Assembly Health Committee passed legislation, authored by Assemblywoman Fiona Ma (D-San Francisco), to protect Californians with life-threatening diseases from escalating insurance costs for medication. The commitee passed Assembly Bill 310 with a 12 to 6 vote after hearing compelling testimony. The bill places a $150 co-payment cap for a one-month supply of medication, as well as prohibits health plans and insurers from using co-insurance and places an annual out-of-pocket limit on prescription drug costs if a plan or insurance policy maintains an annual limit.

AB 310, which is sponsored by the Alliance for Biotherapeutics and the Multiple Sclerosis Society, was introduced in response to health plans that are reclassifying drugs into a new tier and adopting a new method of payment for specialty drugs called co-insurance where a patient pays a percentage of the cost of the drug, as opposed to a traditional co-payment. Specialty drugs are used to treat diseases like multiple sclerosis, rheumatoid arthritis, HIV, cancer, hemophilia, primary immunodeficiency diseases and hepatitis. The bill will now go to the Assembly Appropriations Committee.

"AB 310 is about establishing reasonable cost controls for consumers living with chronic and life-threatening illnesses," said Assemblywoman Ma. "Specialty drug pricing dramatically increases the costs of vital medication, discriminates against the most vulnerable populations and jeopardizes the health of Californians by placing the cost of medications beyond reach. People should not have to choose between bankruptcy or death."

Last year, New York became the first state to pass a bill that prohibited insurers from creating specialty tiers. Other states, including Indiana, Connecticut, Nebraska, Pennsylvania, Rhode Island and Vermont are considering similar legislation. ❖

New Medicare Fee for Institutional Providers

On March 25, the Centers for Medicare and Medicaid Services (CMS) began charging a new application fee to all institutional providers, including nursing homes, hospitals, etc., that are enrolling, re-enrolling, revalidating or adding a new practice location. The fee will be $505 per facility in 2011, but in the future, it will be linked to the Consumer Price Index. The money will be used for "program integrity" efforts, including screening of applicants to the program.

According to CMS, providers should pay the application fee through www.Pay.gov after submitting a completed CMS-855 application. The application fee was included in the final rule implementing Patient Protection and Affordable Care Act provisions to reduce fraud, waste and abuse in Medicare, Medicaid and the Children's Health Insurance Program. ❖

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

Historically, home infusion of subcutaneous immune globulin (SCIG) has been reimbursed by Medicare Part B using the 95 percent of average wholesale price (AWP) methodology. Now that Gamunex-C has an SCIG indication for primary immunodeficiency, will it be covered at the same rate?

Previously approved SCIG products such as Hizentra and Vivaglobin produced by CSL Behring have been reimbursed at 95 percent of AWP using the durable medical equipment (DME) benefit. Gamunex-C should fall under the same formula. However, Gamunex-C presents a unique challenge not previously faced by the Centers for Medicare and Medicaid Services (CMS) when considering immune globulin (IG) products. This is because Gamunex-C has multiple indications and two routes of administration approved by the U.S. Food and Drug Administration. Therefore, the J code of J1561 used for Gamunex-C administered subcutaneously is the same J code used for intravenous (IV) administration of Gamunex-C. As a result, it has taken patience and cooperation to get properly reimbursed.

To explain coverage of Gamunex-C administered subcutaneously, CMS states:

> "Payment for drugs infused through DME at 95 percent of AWP is supported by the Social Security Act, Section 1842(o)(1)(D). Furthermore, the Medicare Claims Processing Manual, Publication 100-04, Chapter 17, Section 20.1.3, states that the payment allowance limits for infusion drugs furnished through a covered item of durable medical equipment on or after January 1, 2005, will continue to be 95 percent of the AWP reflected in the published compendia as of October 1, 2003, unless the drug is compounded or the drug is furnished incident to a professional service. The payment allowance limits for infusion drugs furnished through a covered item of durable medical equipment that were not listed in the published compendia as of October 1, 2003 (for example, new drugs) are 95 percent of the first published AWP unless the drug is compounded or the drug is furnished incident to a professional service."

In response to questions about billing for Gamunex-C for subcutaneous administration, George Oliver, senior director of managed care at Talecris Biotherapeutics, emphasizes the importance of making sure all necessary codes are used when billing CMS. Because Gamunex-C is now approved for new indications, it also has new national drug codes. Therefore, when using Gamunex-C subcutaneously, providers must add a J code modifier. The J code for Gamunex-C administered subcutaneously is J1561-JB. Oliver also cautions that when billing Medicare, it is important to remember that patients must use and providers must bill only for the Freedom 60 pump. Using and/or billing for any other pump will result in a denial of the entire claim. Providers can download a guide to coverage and reimbursement for Gamunex-C at www.gamunex-c.com/media/Gamunex-C_Reimbursement_Guide_GX24-0211.pdf.

Recently, it also was discovered by Karen Schaeck, reimbursement manager at NuFACTOR, the specialty pharmacy division of FFF Enterprises, that while

CMS is reimbursing Gamunex-C at 95 percent of AWP, it is doing so at rates from the published compendia as of Oct. 1, 2003. However, since Gamunex-C is a new product with new indications and new NDC numbers, there is some question about whether the reimbursement rates should be based on the 2003 published rates or the first Redbook publication of AWP that was issued in December 2010. In a step toward correcting the uncertainty, CMS took comments on this issue, as well as others, in a public meeting held May 17. Specific items that were on the agenda and their descriptions that may be of interest to readers of this publication include:

Agenda item 1: Request to establish a code for prestorage pooled, leukocyte reduced, ABO-matched, bacteria tested platelets.

Agenda item 2: Request to establish a new Healthcare Common Procedure Coding System (HCPCS) Level II code for Gammaplex Immune Globulin Intravenous (Human).

Agenda item 3: Request to revise the description of existing HCPCS code J1561 "Injection, Immune Globulin, (Gamunex), Intravenous, Non-Lyophilized (e.g., Liquid), 500 mg" to expand its use for subcutaneous administration and incorporate trade name change from Gamunex to Gamunex-C.

Agenda item 4: Request to establish a separate code for immune globulin (human), trade name: Flebogamma 10% DIF.

Agenda item 6: Request to establish a code for belimumab, trade name: Benlysta.

Agenda item 7: Request to establish a code for alpha1-proteinase inhibitor, trade name: Glassia.

Agenda item 8: Request to discontinue existing code J7184 "Injection, Von Willebrand Factor Complex (Human), Wilate, per 100 IU VWF:RCO" and replace it with a new code for the same product, specifying a different dose descriptor.

Agenda item 9: Request to establish a code for factor XIII concentrate (human), trade name: Corifact, Factor XIII Concentrate (Human).

Agenda item 17: Request to establish a code for sipuleucel-T, trade name: Provenge.

To view summaries of this meeting, go to https://www.cms.gov/MedHCPCSGenInfo/ 08_HCPCSPublicMeetings.asp. ❖

Under the new Affordable Care Act, are private payers required to cover the full cost of vaccines?

While the research is clear that vaccines are the single most cost-effective way to prevent disease, the cost of vaccines still prevents a large percentage of the population from being vaccinated. Historically, many private payers have covered the cost of vaccines recommended by the U.S. Preventive Services Task Force (USPSTF). However, many private insurers also required a copayment or that a deductible be met, and they required vaccines to be administered only in a doctor's office.

But, the new Affordable Care Act requires preventive services such as USPSTF-recommended vaccines to be covered 100 percent with no copayment. This requirement applies to all plans except those that are grandfathered. So, theoretically, more Americans should have access to vaccines because the cost barrier is removed. Yet, how this program will work is in the details of the payers' policies.

A vaccine on the USPSTF-recommended list will be 100 percent covered in a doctor's office. But, whether there is a copayment for that visit will depend on the reason for the visit. If the reason for the visit is preventive care, such as a wellness visit, there should be no copayment. If the visit is for any other reason, the vaccines itself should be covered, but there still may be a copayment, as well as an administration charge for the vaccine.

Payers also have a preferred network for certain services, and in the case of vaccines, patients may not be able to use retail pharmacies to obtain them. Patients wanting to use a retail pharmacy should check with their insurer first to determine if the vaccines will be covered.

To view a list of vaccines covered under the Affordable Care Act, go to http://www.healthcare.gov/law/about/provisions/services/lists.html. ❖

New Blog! Reimbursement Unraveled

In June, the new Reimbursement Unraveled blog debuted at

www.fffenterprises.com/Blogs/Reimbursement

Log on to read the latest about reimbursement issues, and to add your comments. Plus, if you have a reimbursement question, our experts are ready to answer them!

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.

For the treatment of hemophilia A

Take a closer look at Koāte-DVI

Proven efficacy

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

Commitment to safety

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

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

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

Experience

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

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

Important Safety Information

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

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

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

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

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

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

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

Talecris BIOTHERAPEUTICS

Printed in USA November 2009 KD44-1109

Koāte®-DVI

Antihemophilic Factor (Human)

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

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

DESCRIPTION

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

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

PRECAUTIONS

General

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

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

Pregnancy Category C

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

Pediatric Use

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

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

Information for Patient

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

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

ADVERSE REACTIONS

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

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

CAUTION

℞ only

U.S. federal law prohibits dispensing without prescription.

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

08938170-BS

Medicines

New Drug Approved to Treat Melanoma

The U.S. Food and Drug Administration has approved a novel type of cancer vaccine called Yervoy, which works by unleashing the body's own immune system to fight a tumor. In a randomized control trial, patients with metastatic melanoma treated with Yervoy lived a median of about 10 months, compared with 6.4 months for patients in a control group who received a treatment believed to have had little effect. After two years, more than 20 percent of those who got Yervoy, also known as ipilimumab, were alive, compared with 13.7 percent for the control group.

Yervoy is given every three weeks by infusion, and four doses is the typical treatment. Unlike other cancer drugs, such as Provenge, which work by training a patient's immune system to attack the cancer, Yervoy works by disabling a brake on the immune system. And, because it is not specific for any type of tumor, it might conceivably be effective for many types, although that has not been proved in clinical trials. The drawback is that loosening the restraints on the immune system can lead to dangerous side effects, such as colitis, diarrhea, hepatitis, endocrine dysfunction, rashes and eye problems. In the clinical trial of Yervoy, which involved 676 patients, 540 of whom received Yervoy, seven people died of immune-related side effects. ❖

Research

Scientists Design Nanoparticle for Safer and More Effective Vaccine Delivery

Engineers at MIT have designed a new type of nanoparticle that could safely and effectively deliver vaccines for diseases such as HIV and malaria. The new particles, described in the Feb. 20 issue of *Nature Materials*, consist of concentric fatty spheres that can carry synthetic versions of proteins normally produced by viruses. They elicit a strong immune response comparable to that produced by live virus vaccines, but without the safety concerns of live viruses. Such particles could help scientists develop vaccines against cancer, as well as infectious diseases.

In collaboration with scientists at the Walter Reed Army Institute of Research, the MIT engineers are now testing the nanoparticles' ability to deliver an experimental malaria vaccine in mice. In tests with mice, the engineers used the nanoparticles to deliver a protein called ovalbumin, an egg-white protein commonly used in immunology studies. Three immunizations of low doses of the vaccine produced a strong T cell response in the mice, and after immunization, up to 30 percent of all killer T cells in the mice were specific to the vaccine protein.

In addition to the malaria studies, MIT engineers are working on developing the nanoparticles to deliver cancer and HIV vaccines. ❖

Insurance

Raising Medicare Age Would Shift Costs

A report released by the Kaiser Family Foundation says that raising Medicare's eligibility age by two years would save the federal government $7.6 billion, but those costs and more would shift to others. The report assumed full implementation of the health law and an increase in Medicare eligibility to 67 in 2014.

The shift in costs included added out-of-pocket expenses for people ages 65 and 66 that year, higher retiree costs for employers and increased Medicaid costs for states. The total out-of-pocket costs for 65- and 66-year-olds would increase by $5.6 billion, while employer retiree healthcare costs would rise $4.5 billion. The increase in Medicare eligibility also would increase premiums by 3 percent for beneficiaries who stay on the program because younger beneficiaries would be removed from the risk pool. In addition, that shift also would raise prices 3 percent for all individuals who purchase coverage through the law's health insurance exchanges.

Congress is currently considering increasing Medicare's eligibility age as a way to decrease federal spending and extend the solvency of the program. ❖

Did You Know?

"Today, about 3,700 Americans under the age of 20 receive a diagnosis annually of what used to be called 'adult-onset' diabetes."

— Centers for Disease Control Morbidity and Prevention

Medicines

FDA Approves Shingles Vaccine for Ages 50-59

Zostavax, the vaccine manufactured by Merck & Co. to prevent shingles, has been approved by the U.S. Food and Drug Administration for adults ages 50 to 59 years old. Previously, the vaccine had been approved only for adults 60 and older. The widened age group eligible to receive Zostavax is based upon clinical trial data that shows it reduced the risk of outbreaks by 70 percent in adults in that age range. The company says it is investing more than $1 billion to increase manufacturing capacity of Zostavax and other vaccines. ❖

Medicines

India Firm Introduces Generic Breast Cancer Drug

Panacea Biotec, an India-based biotechnology firm, has introduced a generic breast cancer treatment medicine called PacliALL. Developed at the Global Research and Development Center in Navi Mumbai, PacliALL is meant to be used as a chemotherapeutic agent for the treatment of breast cancer, offering patients shorter infusion time and eliminating the need for premedication. According to the company, the drug will be made available at a price that will be nearly 50 percent lower than the competitive products in the domestic and global markets. ❖

Report

New Monograph Published to Increase Tdap Vaccine Rates

A new monograph from The Joint Commission titled "Tdap Vaccination Strategies for Adolescents and Adults, including Health Care Personnel — Strategies from Research and Practice" is intended to help healthcare organizations implement or enhance tetanus, diphtheria and acellular pertussis (Tdap) vaccination programs for adolescents and adults, including healthcare workers who can both acquire pertussis from and spread it to patients, other staff and family members.

The monograph, which includes 17 of the more than 80 submissions from healthcare organizations, has information about pertussis and the Tdap vaccine; barriers to successful Tdap vaccination programs and strategies for overcoming them; evidence-based guidelines and literature that highlight practical Tdap vaccination strategies; and examples of initiatives that organizations have used to establish or enhance their Tdap vaccination programs.

Pertussis is the most common vaccine-preventable childhood disease. However, the Tdap vaccine has been available only since 2005, and information from the Centers for Disease Control and Prevention shows that vaccination rates for adults are very low. Only 16 percent of healthcare workers have been vaccinated.

The monograph can be downloaded free of charge at The Joint Commission's website at www.jointcommission.org. ❖

Research

Protein Identified in Embryo and Disease Development

Scientists at Thomas Jefferson University have discovered that a single protein called FADD (Fas-Associated protein with Death Domain) controls multiple cell death pathways, which could lead to better, more targeted autoimmune disease and cancer drugs. In the study with mice, researchers showed that the protein regulates two types of cell deaths pivotal for embryo and disease development. FADD causes apoptosis, the healthy cell death, while keeping necrosis, the toxic cell death, at bay. The mice that did not express FADD contained raised levels of RIP1 (receptor-interacting protein 1), an important protein that mediates necrosis and the apoptotic process, and their embryonic development failed due to massive necrosis. These findings suggest that with the absence or variation in expression of this one protein, an embryo may not develop properly or a person may develop disease later in life. The study was reported on in the March 2 online edition of *Nature*. ❖

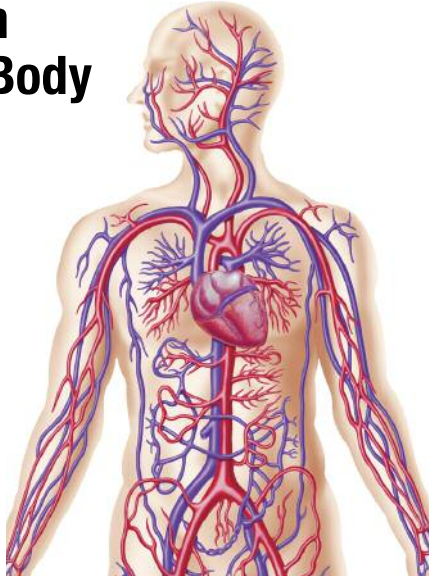
Health Campaign

Federal Officials Launch New Vaccine Strategy

The National Vaccine Program Office has developed a 43-page vaccine plan, the first since 1994, that outlines goals for improving the nation's vaccine system by addressing research and development, supply, financing, distribution, safety, global cooperation and decision-making among consumers and healthcare providers. The plan, which incorporates input from public health officials and medical experts, officials from different levels of government, and the public, also lists 10 implementation priorities that include items such as prioritizing domestic and global vaccine targets, strengthening the scientific base for developing and licensing new flu vaccines, and enhancing the vaccine safety system. The final implementation plan will be completed by the end of 2011. ❖

Research

Study Helps to Explain IG Distribution in the Body



CSL Behring has developed a pharmacokinetic (PK) model that shows how the body absorbs, distributes, metabolizes and eliminates immunoglobulin (IG) following subcutaneous (SC) administration. The PK model provides a new means of simulating the mechanism by which SCIG is transported after it is injected into the subcutaneous tissue, which could affect the volume and frequency of IG dosing for primary immunodeficiency (PI) patients.

Currently, little is understood about the clinical implications of SC versus intravenous (IV) dosing of IG in PI patients, or about where SCIG travels within the body after it is administered and how long it remains there. This new model, which describes a complex system of continuous interactions between extravascular (tissue) and intravascular (blood) compartments that help determine the location and level of SCIG in different parts of the body after injection, shows that fluctuations in serum IgG after IVIG dosing were lower in the first half of the 30-day dosing cycle and higher in the second half of the cycle than would be anticipated. This, then, supports the theory that IgG distribution from the intravascular to the extravascular compartment occurs early in the dosing cycle, with the reverse occurring later in the dosing cycle.

"Clearly, a need exists to better understand the highly complex pharmacokinetic interactions that take place after an infusion of IgG, especially SCIG, in areas of the body that are not traditionally monitored by clinicians," said Stephen Jolles, MD, University Hospital of Wales, Cardiff, U.K. "This new PK model represents a major step toward filling this need, especially for clinicians who measure serum IgG as a means of determining overall levels of IgG, and provides valuable insight into movement of IgG around the body with implications for improving PI patient dosing and treatment." ❖

Vaccine Update

Scientists in Britain have begun the first human trials of a revolutionary cancer vaccine that could save thousands of lives a year. The immune-boosting **leukemia vaccine** will be tried out on volunteers who have either chronic or acute myeloid leukemia, two forms of bone marrow and blood cancer. If successful, the DNA vaccine will be developed at Southampton University.

Researchers at the University of Copenhagen in Denmark have developed a new vaccine that may reduce the number of positive **hepatitis C** tests in the future. They have completed their first successful trial that inoculated animals against the disease.

Medicines

FDA Approves Corifact to Treat Congenital FXIII Deficiency

The U.S. Food and Drug Administration has granted marketing approval for Corifact Factor XIII Concentrate (Human) for the routine prophylactic treatment of congenital factor XIII (FXIII) deficiency. Manufactured by CSL Behring, Corifact, already available in 12 countries throughout the world under the trade name Fibrogammin-P, is the first and only FXIII concentrate approved in the U.S.

Congenital FXIII deficiency, also known as fibrin-stabilizing factor deficiency, is a rare and potentially life-threatening bleeding disorder in which blood clots normally, but the clots formed are unstable, leading to recurrent bleeding. An estimated 150, or one in every two million people, are affected by the condition. ❖

When thrombotic risk is high in hereditary antithrombin deficiency

Proceed Safely

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

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

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

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

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

Important Safety Information

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

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

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

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

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

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

Talecris BIOTHERAPEUTICS

Thrombate III® antithrombin III (human)

Printed in USA November 2009 TH86-1109

THROMBATE III®
Antithrombin III (Human)

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

FOR INTRAVENOUS USE ONLY

DESCRIPTION

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

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

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

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

INDICATIONS AND USAGE

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

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

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

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

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

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

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

PRECAUTIONS

General

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

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

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

Laboratory Tests

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

Drug Interactions

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

Pregnancy Category B

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

Pediatric Use

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

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

ADVERSE REACTIONS

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

CAUTION

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Research

Vaccine Safety Dominates Office Visit Concerns

Primary care physicians need considerable help winning the vaccine war given the limited amount of time they have to make their case in the exam room, according to the authors of a new study published online April 15 in the *American Journal of Preventive Medicine*. Fifty-three percent of family practice physicians and pediatricians surveyed in 2009 reported spending 10 to 19 minutes on vaccine discussions when parents harbor "substantial concerns" about adverse effects, and another 8 percent reported conversations of 20 minutes or longer. Eight percent of physicians report vaccination refusals for 10 percent or more of children per month, and 79 percent say it happens at least once a month, mostly due to concerns about long-term complications and autism.

About three-quarters of physicians think parents are acting responsibly when they question whether their child should be vaccinated, and roughly two-thirds do not feel disrespected when parents disregard their recommendations. However, many physicians are taking steps to protect themselves. Forty-four percent always or often require parents to sign a waiver if

they decline vaccination, and one in 10 always or often dismisses such families from their practice if they refuse vaccines in the primary series. ❖

People and Places in the News

FDA APPROVALS

Grifols has received FDA approval to revise its labeling for Alphanate Antihemophilic Factor/von Willebrand Factor Complex (Human) indicating that certain manufacturing steps have been shown to reduce the infectivity of an experimental TSE agent that is a model for variant Creutzfeldt Jakob Disease (vCJD). The labeling revisions stem from extensive Grifols research into the capacity for various manufacturing steps to eliminate a TSE experimental model agent.

Dendreon Corp. has received clearance from the FDA to expand manufacturing facilities for its cancer vaccine Provenge in the U.S. The company's New Jersey facility, which is currently operating at 25 percent capacity with 12 workstations, can now be fully operational with 48 workstations. The company also is building additional capacity in its Atlanta, Ga., and Los Angeles facilities, each of which will have 36 workstations. Dendreon expects to have 500 centers where patients can be treated with Provenge by the end of 2011, well above the current 50 centers.

APPOINTMENTS

Sandra Haberichter, PhD, has joined BloodCenter of Wisconsin as director of the Hemostasis Reference Laboratory. Prior to joining BloodCenter, Dr. Haberichter worked at the Medical College of Wisconsin for more than eight years as assistant professor in the department of pediatrics.

Dr. **Aldar Bourinbaiar**, a co-founder of Immunitor Inc., has joined Immune Network Ltd.'s board of directors. Immune Network is completing its acquisition of 50 percent of Immunitor, a company that has global rights to a patented product called V5, clinically shown to be effective against hepatitis B, hepatitis C and recently demonstrated as a potent immune adjunct for chemotherapeutic management of tuberculosis.

ACQUISITIONS/ALLIANCES

Spain's **Grifols SA** has acquired **Talecris Biotherapeutics** for $3.4 billion, becoming a global producer of plasma protein therapies. It is estimated that the deal will generate $230 million of synergies from a more efficient network and optimized sales, marketing and research.

Sanofi-aventis has entered into a research collaboration with **Columbia University Medical Center** to develop innovative diabetes medicines. The three-year research collaboration, with the laboratory of Dr. Gerard Karsenty, will investigate the role of the osteoblast-secreted peptide, osteocalcin, in diabetes management.

Gilead Sciences Inc., Foster City, Calif., is buying **Calistoga Pharmaceuticals Inc**. for $375 billion. Calistoga makes drugs that target diseases such as autoimmune disease, hematological cancers, non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

Biothera has acquired the anti-cancer monoclonal antibody AS1402 from **Antisoma** for undisclosed terms. AS1402 targets an aberrant form of the cell-surface protein MUC1 that is widely expressed in many types of cancer. ❖

Global Vaccines

Improving Vaccination Rates Around The World

The progress made to improve vaccination rates around the world is astounding, made possible through the cooperation and funding of many organizations, but much still needs to be done to decrease or eradicate vaccine-preventable diseases.

By Amy Scanlin, MS

Each year, nearly 2.5 million children die worldwide from vaccine-preventable diseases (VPDs). The millions who do survive after contracting one of these diseases often are left severely impaired. Despite the fact that vaccination rates throughout the world are at an all-time high, 21 percent of children still don't receive them.[1] Yet, for a cost of just a few dollars per child, immunizations could be administered, millions of lives could be saved, and millions more could avoid the resulting disabilities.

U.S. Vaccination Efforts

Although the United States spends more than any other country on healthcare, the uninsured and underinsured (often represented by low-income, racial and ethnic minorities) continue to encounter barriers to receiving preventive and primary care. In turn, they suffer from some of the highest rates of disease, including obesity, cancer and AIDS. More than one in three American Indians and Hispanics and just under one in five African-Americans are uninsured, compared with one in eight Caucasians. Four in 10 low-income Americans are uninsured and about one-third of these have chronic diseases. And, while more than $2.2 trillion was spent on healthcare in 2007 alone, the gap in coverage is growing and, along with it, the incidence of disease.[2]

That being said, there is a positive side to immunization for America's youth. The Centers for Disease Control and Prevention (CDC) reports that immunization rates for VPDs are high in the U.S. — about 90 percent for children between the ages of 19 months and 35 months. Fewer than 1 percent of young children fail to receive vaccinations at all.[3] In fact, the majority of objectives set forth in Healthy People 2010 were met in the area of early childhood vaccinations.[4]

Also encouraging is a report that teen vaccination rates are on the rise, although slowly, particularly for the tetanus-diphtheria-acellular pertussis (Tdap) and meningococcal conjugate vaccines, according to the CDC's National Immunization Survey. There also has been an increase in teen girls receiving their first of three doses of the human papillomavirus (HPV) vaccine. Interestingly, the rate of vaccination for HPV was statistically higher in low-income areas. And, while there is no racial or ethnic difference in girls getting one dose of the vaccine, rates are lower for African-Americans and Hispanics than for whites when it comes to receiving all three doses.[5]

Overall, the rates of vaccination levels are improving for adolescents, but progress continues to be needed. The same is true for adults. Though vaccination rates are slowly on the rise, once children reach adulthood, these rates drop. For instance, the CDC says only one-third of adults receive flu shots, only 10 percent of adults over age 60 have received the shingles vaccine, and only 17 percent of women ages 19 through 26 have received the HPV vaccine. Further, the CDC says that 95 percent of VPDs occur in adults.

Steps to Improve U.S. Vaccination Rates and Subsequent Barriers

In the late 1970s and early 1980s, major efforts were undertaken to improve vaccination rates, which at that time were extremely low — by some estimates as low as 20 percent in inner cities. The Childhood Immunization Initiative was established in 1993, which, with the help of unprecedented federal resources, increased coverage in preschool children to record high levels. So much so that in 1997, President Clinton announced that childhood vaccination goals had been exceeded.[6]

It is feared, however, that the huge successes in eradicating some diseases and significantly lessening the incidence of others through vaccinations may have put the dangers of VPDs in the back of people's minds, therefore downplaying the necessity of receiving vaccines. "Vaccines are a victim of their own success," says Amy Caruso, public information officer with the North Carolina Immunization Branch of the Department of Health and Human Services. "When people don't see the impact of certain diseases, it can be easy to forget how dangerous they are. This challenge will persist as more vaccines are developed and diseases that cause sickness and death today fade from our collective memory." Increased education on VPDs, the availability and safety of vaccines, as well as improved access all are necessary to maintain the progress made in these areas.

For a cost of just a few dollars per child, immunizations could be administered, millions of lives could be saved, and millions more could avoid the resulting disabilities.

Initiatives to maintain vaccine awareness vigilance include the implementation of immunization information systems and electronic health records to expand the confidential, computerized population-based registries of immunizations for each patient, as well as reminder calls by providers when vaccines are due. The 2010 National Vaccine Plan includes improved communication as one of its five goals for the next decade.

Though efforts to increase vaccination rates have been successful, barriers continue to exist in some areas, resulting in part of the population failing to receive some or all of their necessary immunizations. A major barrier is the cost of vaccinations — particularly for the low-income population — which is exacerbated by the fact that private healthcare plans sometimes only partially cover vaccines and other times don't cover them at all.

At present, each state has the option to choose whether to

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About AFLURIA

AFLURIA is an inactivated influenza virus vaccine indicated for active immunization of persons ages 6 months and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.

This indication is based on the immune response elicited by AFLURIA; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with AFLURIA.

Administration of CSL's 2010 Southern Hemisphere influenza vaccine has been associated with increased postmarketing reports of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years.

Select Safety Information

AFLURIA is contraindicated in individuals with hypersensitivity to eggs, neomycin, or polymyxin, or in anyone who has had a life-threatening reaction to previous influenza vaccination.

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

If AFLURIA is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Antibody responses in geriatric subjects were lower after administration of AFLURIA in comparison to younger adult subjects.

In adults, the most common local (injection-site) adverse reactions observed in clinical studies with AFLURIA were tenderness, pain, redness (erythema), and swelling. The most common systemic adverse reactions observed were headache, malaise, and muscle aches (myalgia).

In children, the most common local (injection-site) adverse reactions observed in a clinical study with AFLURIA were pain, redness, and swelling. The most common systemic adverse reactions observed were irritability, rhinitis, fever, cough, loss of appetite, vomiting/diarrhea, headache, muscle aches and sore throat.

Vaccination with AFLURIA may not protect all individuals.

Please see the brief summary of the Prescribing Information on the following page.

afluria®
INFLUENZA VIRUS VACCINE

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Brief Summary of Prescribing Information for AFLURIA® (Influenza Virus Vaccine)

INDICATIONS AND USAGE

AFLURIA is an inactivated influenza virus vaccine indicated for active immunization of persons ages 6 months and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.

This indication is based on the immune response elicited by AFLURIA; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with AFLURIA.

DOSAGE AND ADMINISTRATION

Children

Children 6 months through 35 months of age not previously vaccinated with an influenza vaccine, or vaccinated for the first time last season with only one dose, should receive two 0.25 mL doses: one on day 1 followed by another approximately 4 weeks later. Children 6 months through 35 months of age given two doses of any influenza vaccine last season, or at least one dose two or more years ago, should receive only one 0.25 mL dose.

Children 36 months through 8 years of age not previously vaccinated with an influenza vaccine, or vaccinated for the first time last season with only one dose, should receive two 0.5 mL doses: one on day 1 followed by another approximately 4 weeks later. Children 36 months through 8 years of age given two doses last season, or at least one dose two or more years ago, should receive only one 0.5 mL dose.

Children 9 years of age and older should receive a single 0.5 mL intramuscular dose.[1]

The preferred sites for intramuscular injections are the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in toddlers and young children.

Adults

AFLURIA should be administered as a single 0.5 mL intramuscular injection, preferably in the deltoid muscle of the upper arm.

CONTRAINDICATIONS

AFLURIA is contraindicated in individuals with known hypersensitivity to eggs, neomycin, or polymyxin, or in anyone who has had a life-threatening reaction to previous influenza vaccination.

WARNINGS AND PRECAUTIONS

Fever and Febrile Seizures

Administration of CSL's 2010 Southern Hemisphere influenza vaccine has been associated with increased postmarketing reports of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years.

Guillain-Barré Syndrome (GBS)

If GBS has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks.

Altered Immunocompetence

If AFLURIA is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Limitations of Vaccine Effectiveness

Vaccination with AFLURIA may not protect all individuals.

ADVERSE REACTIONS

Overall Adverse Reactions

Serious allergic reactions, including anaphylactic shock, have been observed during postmarketing surveillance in individuals receiving AFLURIA. Administration of CSL's 2010 Southern Hemisphere influenza vaccine [formulated to contain A/California/7/2009 (H1N1), A/Wisconsin/15/2009 (H3N2) and B/Brisbane/60/2008 (B Strain)] has been associated with increased postmarketing reports of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years.

In adults, the most common local (injection-site) adverse reactions observed in clinical studies with AFLURIA were tenderness, pain, redness (erythema), and swelling. The most common systemic adverse reactions observed were headache, malaise, and muscle aches (myalgia).

In children, the most common local (injection-site) adverse reactions observed in a clinical study with AFLURIA were pain, redness and swelling. The most common systemic adverse reactions observed were irritability, rhinitis, fever, cough, loss of appetite, vomiting/diarrhea, headache, muscle aches and sore throat.

Safety Experience from Clinical Studies

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

Clinical data for AFLURIA have been obtained in four clinical studies, three in adult populations (Studies 1 to 3) and one in a pediatric population (Study 4).

Clinical safety data are provided for two of the adult studies (Studies 1 and 2) and one pediatric study (Study 4). Rates of solicited fever in children from a second pediatric study (Study 5) are also provided.

A US study (Study 1) included 1,357 subjects for safety analysis, ages 18 to less than 65 years, randomized to receive AFLURIA (1,089 subjects) or placebo (268 subjects). There were no deaths or serious adverse events reported in this study.

A UK study (Study 2) included 275 subjects, ages 65 years and older, randomized to receive preservative-free AFLURIA (206 subjects) or a European-licensed trivalent inactivated influenza vaccine as an active control (69 subjects). There were no deaths or serious adverse events reported in this study.

An open-label, uncontrolled study in children, conducted in Australia (Study 4), included 298 subjects, ages 6 months to less than 9 years. All subjects received preservative-free AFLURIA administered as two doses, one month apart. Subjects were subdivided into two age groups: children ages 6 months to less than 3 years (151 subjects) received two 0.25 mL doses of AFLURIA and children ages 3 years to less than 9 years (147 subjects) received two 0.5 mL doses of AFLURIA. There were no deaths or vaccine-related serious adverse events reported in this study.

The safety assessment was identical for the two adult studies. Local (injection-site) and systemic adverse events were solicited by completion of a symptom diary card for 5 days post-vaccination. Unsolicited adverse events were collected for 21 days post-vaccination.These unsolicited adverse events were reported either spontaneously or when subjects were questioned about any changes in their health post-vaccination. All adverse events are presented regardless of any treatment causality assigned by study investigators.

In the open-label pediatric study (Study 4), solicited adverse events were recorded for up to 7 days and unsolicited adverse events were recorded for 30 days post-vaccination. Data are presented following each dose for each age group. All adverse events are presented regardless of any treatment causality assigned by study investigators.

Rates of solicited fever in the seven days following vaccination with the 2009-2010 formulation of AFLURIA or another U.S. licensed influenza vaccine (manufactured by Sanofi Pasteur, Inc.) in children 6 months to less than 18 years of age (Study 5) appear in next column.

Proportion of Subjects With Solicited Local or Systemic Adverse Events Within 5 Days After Administration of AFLURIA, Irrespective of Causality

The most commonly reported solicited adverse reactions (>20%) in Study 1 (subjects ≥18 to <65 years) with AFLURIA were headache, pain, and tenderness, and in Study 2 (subjects ≥65 years) were redness and tenderness.

Adverse Events Reported Spontaneously by ≥1% of Subjects Within 21 Days After Administration of AFLURIA, Irrespective of Causality (Studies 1 and 2, Adult Populations)

Reactions reported in greater than 1% of adults: Study 1: headache, pharyngolaryngeal pain, reactogenicity event, diarrhea, back pain, upper respiratory tract infection; Study 2: headache, nasal congestion, cough, rhinorrhea, pharyngolaryngeal pain, back pain.

Proportion of Subjects With Solicited Local or Systemic Adverse Events Within 7 Days After Administration of AFLURIA, Irrespective of Causality (Study 4, Pediatric Population, ages 6 months to 9 years) Reactions reported in greater than 10% of subjects ≥6 months to <3 years, Dose 1 and Dose 2: Systemic—irritability, rhinitis, fever, cough, loss of appetite, vomiting/diarrhea; Local—swelling, erythema, pain. Reactions reported in greater than 10% of subjects ≥3 years to < 9 years, Dose 1: Systemic—irritability, rhinitis, fever, cough, headache, myalgia; Local—Pain erythema, swelling. Dose 2: Systemic—irritability, rhinitis, cough, headache, sore throat; Local—pain, erythema, swelling.

Adverse Events Reported Spontaneously by ≥5% of Subjects Within 30 Days After Administration of AFLURIA, Irrespective of Causality (Study 4, Pediatric Population)

Reactions reported in greater than 5% of subjects ≥6 months to <3 years, Dose 1: nasopharyngitis, rhinitis, upper respiratory tract infection, cough, rhinorrhea, teething, vomiting, influenza-like illness. Dose 2: nasopharyngitis, rhinitis, upper respiratory tract infection, irritability, cough, rhinorrhea, teething, influenza-like illness, pyrexia. Reactions reported in greater than 5% of subjects ≥3 to <9 years, Dose 1: nasopharyngitis, rhinitis, upper respiratory tract infection, headache, cough, rhinorrhea, influenza-like illness; Dose 2: nasopharyngitis, rhinitis, upper respiratory tract infection, cough.

Proportion of Subjects With Solicited Fever Within 7 Days of Vaccination With AFLURIA or US Licensed Comparator Vaccine (Study 5 Pediatric Population)

6 months to < 3 years, Dose 1: AFLURIA 37%, Comparator 14%; Dose 2: AFLURIA 15%, Comparator 14%; 3 to <5 years, Dose 1: AFLURIA 32%, Comparator 11%; Dose 2: AFLURIA 14%, Comparator 16%; 5 to < 9 years, Dose 1: AFLURIA 16%, Comparator 9%; Dose 2: AFLURIA 0%, Comparator 2%; 9 to < 18 years, Dose 1: AFLURIA 6%, Comparator 4%.

Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The adverse reactions described have been included in this section because they: 1) represent reactions that are known to occur following immunizations generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been reported frequently. These adverse reactions reflect experience in both children and adults and include those identified during post-approval use of AFLURIA outside the US since 1985.

Blood and lymphatic system disorders

Transient thrombocytopenia

Immune system disorders

Allergic reactions including anaphylactic shock and serum sickness

Nervous system disorders

Neuralgia, paresthesia, and convulsions (including febrile seizures); encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

Vascular disorders

Vasculitis with transient renal involvement

Skin and subcutaneous tissue disorders

Pruritus, urticaria, and rash

Other Adverse Reactions Associated With Influenza Vaccination

Anaphylaxis has been reported after administration of AFLURIA. Egg protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, asthma, and systemic anaphylaxis.

The 1976 swine influenza vaccine was associated with an increased frequency of 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 one additional case per 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.

DRUG INTERACTIONS

Concurrent Use With Other Vaccines

There are no data to assess the concomitant administration of AFLURIA with other vaccines. If AFLURIA is to be given at the same time as another injectable vaccine(s), the vaccine(s) should be administered at different injection sites. AFLURIA should not be mixed with any other vaccine in the same syringe or vial.

Concurrent Use With Immunosuppressive Therapies

The immunological response to AFLURIA may be diminished in individuals receiving corticosteroid or immunosuppressive therapies.

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Nursing Mothers

AFLURIA has not been evaluated in nursing mothers. It is not known whether AFLURIA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AFLURIA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of AFLURIA in children below 6 months of age have not been established. The safety and immunogenicity of AFLURIA was evaluated in 298 children between the ages of 6 months and 9 years (Study 4). In this study the incidence of fever in children 6 months to < 3 years of age following the first and second doses of AFLURIA was 23%. Among children 3 years to < 9 years of age the incidence was 16% following the first dose and 8% following the second dose. Administration of CSL's 2010 Southern Hemisphere influenza vaccine has been associated with increased postmarketing reports of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years.

Geriatric Use

In four clinical studies, 343 subjects ages 65 years and older received AFLURIA. Hemagglutination-inhibiting antibody responses in geriatric subjects were lower after administration of AFLURIA in comparison to younger adult subjects. Adverse event rates were generally similar in frequency to those reported in subjects ages 18 to less than 65 years, although some differences were observed.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied	**NDC Number**
Package of ten 0.5 mL single-dose, prefilled syringes without needles	33332-010-01
Package of one 5 mL multi-dose vial, which contains ten 0.5 mL doses	33332-110-10

Store refrigerated at 2° - 8°C (36° - 46°F). Do not freeze. Protect from light. Do not use AFLURIA beyond the expiration date printed on the label.

Manufactured by: CSL Limited, Parkville, Victoria, 3052, Australia, US License No. 1764

Distributed by: Merck Sharp & Dohme Corp., a subsidiary of **MERCK & CO., INC.,** Whitehouse Station, NJ 08889, USA

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cover vaccinations under Medicaid. However, under the new healthcare law, Medicaid is being expanded and vaccinations are considered an "essential health benefit." A potential loophole is that coverage of vaccinations is not required for those already enrolled in Medicaid. Other loopholes exist from state to state, such as those allowing exemptions for self-insured employer groups from providing no-cost vaccines.

Qualified adults who have Medicare Part B may receive the influenza, pneumococcal and hepatitis B vaccines (for those at medium to high risk of contraction), provided their doctor's office accepts assignment. Other vaccinations are typically not covered under Medicare.

The new healthcare law will require all new health plans to include the cost of vaccinations recommended by the Advisory Committee on Immunization Practices (ACIP) in full. However, Medicare will not include the full cost of vaccines, and because most vaccines fall under Medicare Part D, they may not be available in doctors' offices. Instead, they must be prescribed, picked up at a pharmacy and returned to the physician's office for administration, which is not recommended for a variety of reasons.

Though vaccination rates are slowly on the rise, once children reach adulthood, these rates drop.

As the specifics of the healthcare law continue to be hammered out and implemented, the states are working hard in the meantime to make sure funding is readily available for immunizations. As Caruso explains: "Because immunizations are a preventive measure, the cost associated with support for immunization campaigns far outweighs the cost associated with treating the diseases vaccines prevent. The Centers for Disease Control and Prevention, which provides funding for the Vaccines for Children program, is committed to vaccines, and we feel confident that commitment will persist."

Educational Efforts to Improve U.S. Vaccination Rates

Even though VPDs are at record low levels, it continues to be a challenge to educate the population about vaccinations. According to the Centers for Medicare and Medicaid Services (CMS), this becomes especially important for those who do not receive routine primary care. Some educational efforts include Adolescent Immunization Month, observed in April, and National Immunization Awareness Month, which is in August. Both events provide a starting point for communication between providers and patients about the importance of ensuring patient vaccines are up to date. Another effort, which some states have in place, include specific programs to educate clinicians about how to talk with patients about routine vaccinations.

More recently, novel approaches to educate the public have been launched, such as the Facebook application to "educate, motivate and mobilize people to prevent the spread of HPV."[7] Developed by the Partnership for Prevention and the University of Maryland College of Information Studies, users can take interactive quizzes, get information on prevention and anonymously share the link with friends.

Other proposals being considered include requiring adolescents who attend childcare programs, schools and colleges be vaccinated to not only limit the spread of disease, but to educate parents about the importance of immunizations. Educational materials provided to schools and clinicians offer guidance on necessary vaccines at each age level and provide talking points for providers and patients. As an example, "West Virginia is doing a lot of education and awareness raising," says Jeffrey J. Neccuzi, director of the West Virginia Department of Health and Human Resources Division of Immunization Services. "The state's Division of Immunization Services is conducting the 7th Grade Vaccination Initiative this 2010-11 school year in which Tdap and meningococcal vaccinations have been offered to seventh-grade students in schools across the state, not only to get seventh-grade students up-to-date, but also to call attention to the need for adolescent vaccination."

Still, even with educational efforts, the Internet is rife with misinformation that travels quickly and, in some cases, counters the good efforts of educators. Says Neccuzi: "[Our] biggest challenge has been to maintain public confidence in vaccines, while groups and individuals have been using the Internet and mass media to make sensationalized, misleading and even outright false claims concerning vaccine safety. Hopefully, the falsehood that vaccines cause autism has been debunked for good."

Vaccines for Children: Administration in the U.S.

Started in 1994, the Vaccines for Children (VFC) program provides vaccinations at no cost to children under the age of 19 who are uninsured or underinsured through its more than 40,000 enrolled physicians. Vaccines recommended by ACIP and approved by the CDC are provided directly to providers and clinics enrolled in the program at no cost. To receive the vaccines, children must visit a Federally Qualified Health Center or Rural Health Clinic, which meet certain criteria for

Medicare and Medicaid programs.

Each state or territory health department is responsible for administering its VFC program. Those eligible to receive free vaccines under the program include children who are uninsured, underinsured, Medicaid-eligible, American Indian or native Alaskan. While there is no charge for the vaccine itself because it has already been paid for by federal tax dollars, some doctors may charge an office visit or administration fee. However, should that fee be prohibitive, the fee must be waived.

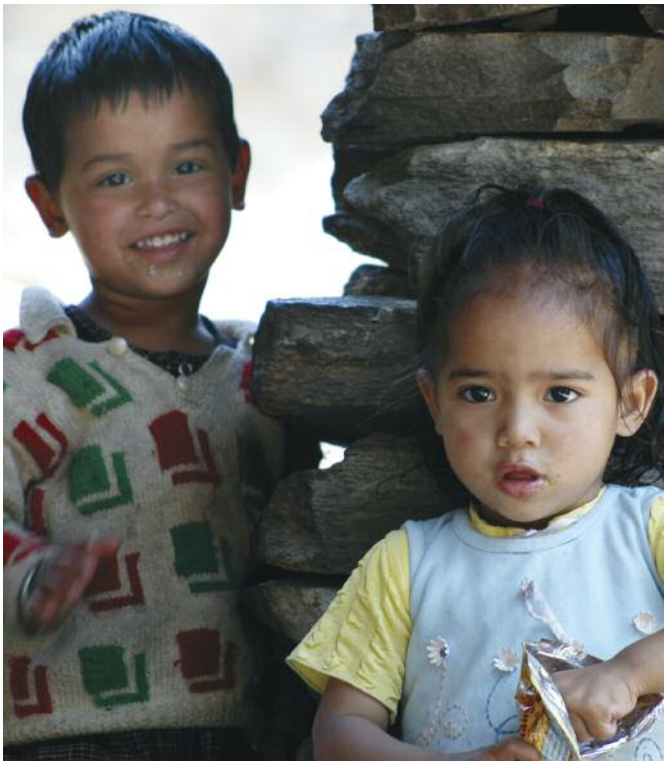
At present, each state has the option to choose whether to cover vaccinations under Medicaid.

The VFC program is widely accessible in the U.S. through most pediatricians, many family practice offices and those schools that have enrolled. In all, there are more than 44,000 VFC-approved locations.[8] Thanks to VFC and the Medicaid program, it is estimated that 70 percent of children receive their vaccinations in the private medical sector.[9]

The barriers to immunizations for adolescents in the U.S. appear to be low, due in part to the VFC program. However, fewer teens are receiving recommended vaccinations, indicating room for improvement in reaching this group. Education about the importance of and access to vaccines will play a large role in making these improvements.

Worldwide Vaccination Efforts

Globally, increased access to vaccinations has saved more than 20 million children and is considered to be one of the biggest success stories in global public health. Measles and polio are two significant examples of this success. The death rate due to measles in children has declined 75 percent since the year 2000,[10] while measles immunization rates have increased to 82 percent worldwide since 1990. Even the poorest regions have seen improvements in measles immunization rates: 74 percent coverage today, which is up from 56 percent in 2000. Since the implementation of the Global Polio Eradication Initiative, polio vaccine rates have increased dramatically, and the incidence of disease has been reduced from 350,000 cases in 1988 to 1,652 cases in 2008.



The United Nations' (U.N.) Millennium Development Goal is to reduce the under-5-year-old mortality rate by two-thirds by 2013. In addition to substantial efforts by the U.N., individual nations, agencies and global nonprofits with the goal of improving global health are assisting with funding and coordination efforts. One such nonprofit, the Bill and Melinda Gates Foundation, has partnered with organizations such as the Global Alliance for Vaccines and Immunisation (GAVI), the World Health Organization (WHO), the Sabin Vaccine Institute, and Agence de Médecine Preventive with a goal of increasing immunization rates to 90 percent worldwide, reducing death from measles by 90 percent and eradicating polio.[11]

Established in 1974 through a WHO Assembly resolution that promotes vaccine distribution to children worldwide, the Expanded Program on Immunization (EPI) provides immunizations to the underserved. When initiated, less than 5 percent of the world's children had been vaccinated against six targeted diseases: diphtheria, whooping cough, tetanus, measles, poliomyelitis and tuberculosis. In the years since, additional vaccines have been added to routine infant immunization schedules, including hepatitis B, Haemophilus influenzae type b (Hib) and yellow fever. Many countries also are adding the pneumococcal conjugate and rotavirus vaccines.[12] Today, nearly 80 percent of children are vaccinated before their first birthday, thanks to partnerships between the Economic Policy Institute, UNICEF, host countries and the GAVI Alliance.[10] In addition, new technologies and strategies are improving access to vaccines, including a pentavalent vaccine that allows children to be vaccinated against diphtheria, tetanus, pertussis, HepB, and Hib (DPT-HepB+Hib) all at once.

Developing countries also are learning to better understand their own health concerns. For instance, they are developing surveillance systems to determine which diseases are most prevalent and, in turn, which vaccines are most needed. And, they are raising awareness and funds, both public and private, to generate the necessary resources.

It used to take as long as 20 years for a vaccine that was available in affluent countries to become available in developing countries, but that timeline has been compressed. It is hoped that with commitment from all parties involved, including manufacturers, world partners and individual countries, that vaccines may soon be introduced simultaneously around the world.[10] This is especially important now that international travel has become more accessible in many parts of the world. Vaccinating all populations will better protect every nation from disease.

Transportation Challenges to Vaccination

Aside from the high production costs of newer, more technologically advanced and often single-dose syringe vaccines, the cost of transporting vaccines to their destinations, often in the most remote areas of developing nations where infrastructure is limited, is a huge barrier to global vaccination.

Globally, increased access to vaccinations has saved more than 20 million children and is considered to be one of the biggest success stories in global public health.

One way to reduce high rates of waste from spoilage and travel/maintenance costs is to improve the 30-year-old transportation system through the use of a continuously controlled temperature environment from manufacturer to recipient. Optimize: Immunization Systems and Technologies for Tomorrow, a collaboration between WHO and PATH, a global nonprofit organization, has been tasked with formulating

ideas for improving upon this supply chain. One idea being explored is the use of cooled carts (currently used to transport produce in European countries) to move vaccines from place to place in developing countries. The cost savings of using vaccine cold boxes could be considerable, because these carts are capable of handling a much larger quantity of vaccines. Optimize envisions a state-of-the-art supply chain by 2025 that meets "the changing needs of a changing world in order to enable the right vaccines to be in the right place, at the right time, in the right quantities, in the right condition, and at the right cost."[13]

New technologies in development have the potential of producing cost-effective vaccines for a variety of populations and diseases.

Also being explored by this collaboration are options such as incentives for manufacturing companies to make products available for developing countries, while ensuring local leaders understand the importance and value of vaccinations.

Emerging Threats to Global Vaccination

Vaccines that target diseases more prevalent in developing countries are currently in the research and development stage, including group A meningococcal meningitis (prevalent in sub-Saharan Africa), as well as a new vaccine for malaria. Yet, even as these vaccines are researched, changing pathogens result in new threats and new strains of disease. Since the 1970s, newly emerging diseases have been discovered at a rate of about one per year, according to the *2007 World Health Report*. And, as our society travels more easily and readily across lands and borders, new threats are a problem for all, not just developing nations with less access to healthcare. Pockets of unvaccinated people especially become at risk for larger-scale health concerns and subsequent spread of disease.

New technologies in development have the potential of producing cost-effective vaccines for a variety of populations and diseases. Controlling particle size in the manufacturing process, using insect cells to express influenza proteins and create virus-like particles, and even developing a recombinant influenza vaccine technology based on combining influenza and bacteria proteins are some options being explored.[14]

Even as new technologies for improving the production and transportation of vaccines are discovered and introduced, many challenges remain. Funding is one of the biggest challenges because without adequate support, the momentum of these programs cannot be sustained. Additional vaccines are being developed, and these newer, more advanced vaccines are often more expensive to produce and transport via appropriate temperature-controlled environments to the most remote areas of the world. WHO and UNICEF estimate that an additional $11 billion to $15 billion will be needed to maintain the momentum with current and newly introduced vaccines to reduce VPDs by 2015.[10]

At the 2010 World Economic Forum, the Bill and Melinda Gates Foundation called for a "Decade of Vaccines." Resources around the world have come together with the purpose of improving health and saving lives from illnesses caused by VPDs. And, while there is much more still to be done, the advances in just the last 20 years are astounding. ❖

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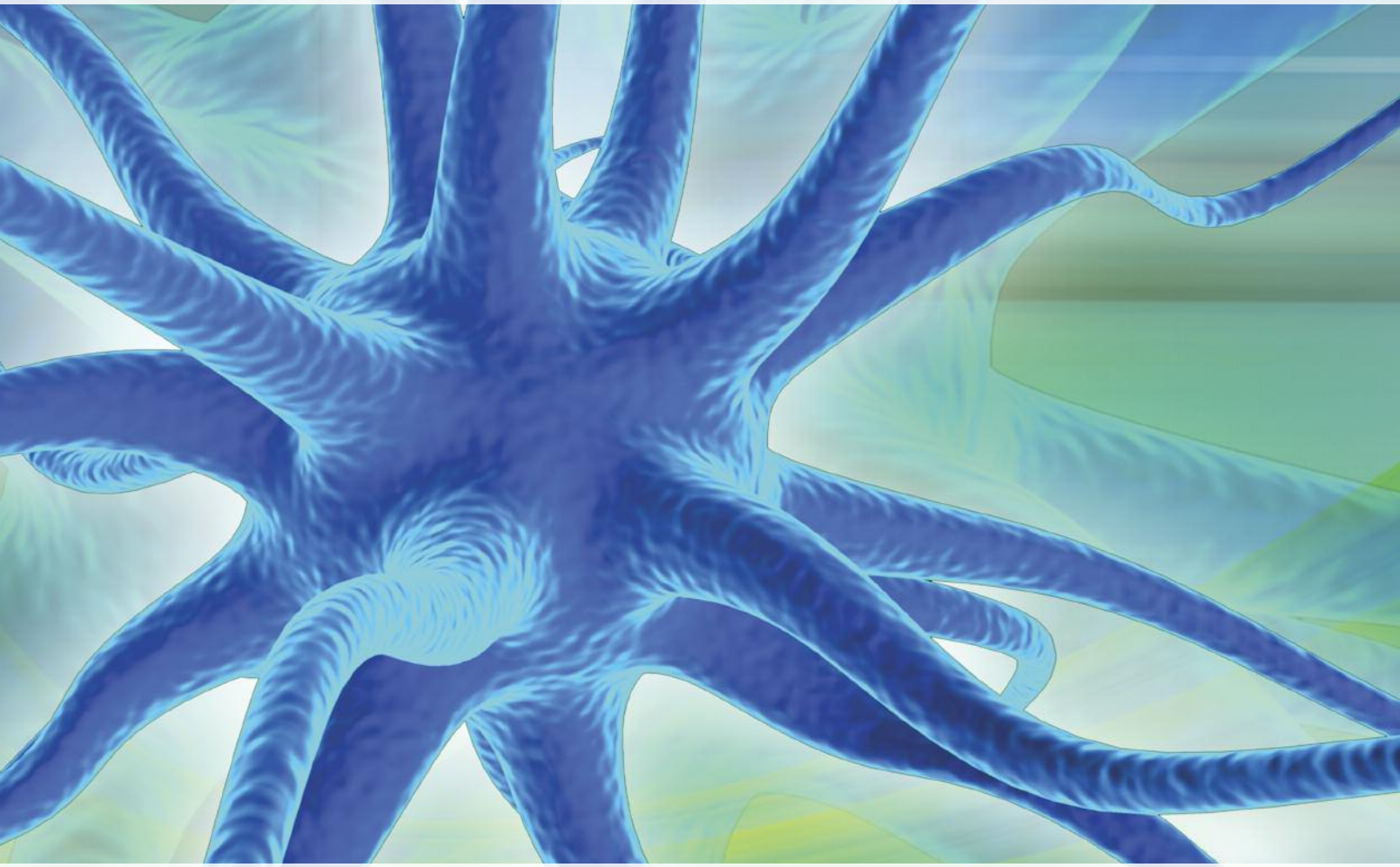
References

1. Gates Foundation. Vaccine Overview. Accessed at www.gatesfoundation.org/vaccines/Pages/overview.aspx.
2. Health Disparities: A Case for Closing the Gap. HealthReform.gov. Accessed at www.healthreform.gov/reports/healthdisparities/index.html.
3. Centers for Disease Control and Prevention. CDC Survey Finds Childhood Immunization Rates Remain High. Sep. 16, 2010. Accessed at www.cdc.gov/media/pressrel/2010/r100916.htm
4. Setse, RW, Euler, GL, Gonzalez-Feliciano, AG, Bryan, LN, Furlow, C, Weinbaum, CM, and Singleton, JA. Influenza Vaccination Coverage — United States 2000-2010. *Morbidity and Mortality Weekly Report (MMWR)*, Jan. 14, 2011. Accessed at www.cdc.gov/mmwr/preview/mmwrhtml/su6001a7.htm?s_cid=su6001a7_e%0d%0a.
5. Centers for Disease Control and Prevention. Teen Vaccination Rates Increasing Across the U.S. Aug. 19, 2010. Accessed at www.cdc.gov/media/pressrel/2010/r100819b.htm.
6. Development of Community and State Based Immunization Registries. Report of the National Vaccine Advisory Committee (NVAC), Jan. 12,1999. Accessed at: www.cdc.gov/vaccines/programs/iis/pubs/nvac.htm.
7. Partnership for Prevention. Partnership, U-Md. Develop Novel Facebook Application to Prevent Cervical Cancer. Oct. 12, 2009. Accessed at www.prevent.org/NewsRoom/default.aspx?id=88.
8. Centers for Disease Control and Prevention. VFC Program: Vaccines for Uninsured Children. Where Can I Get Vaccines? Accessed at www.cdc.gov/vaccines/programs/vfc/parents/default.htm#where.
9. Development of Community and State Based Immunization Registries. Report of the National Vaccine Advisory Committee (NVAC), Jan. 12,1999. Accessed at: www.cdc.gov/vaccines/programs/iis/pubs/nvac.htm.
10. Bill and Melinda Gates Foundation. Progress Sheet: Progress towards Immunization — Winning the Fight Against Deadly Diseases. Accessed at www.gatesfoundation.org/livingproofproject/Documents/progress-towards-immunization.pdf.
11. Bill and Melinda Gates Foundation. Vaccine Overview. Accessed at www.gatesfoundation.org/vaccines/Pages/overview.aspx#.
12. World Health Organization. Expanded Programme on Immunization (EPI). Accessed at www.who.int/immunization_delivery/en/.
13. Optimize: Immunization Systems and Technologies for Tomorrow. Immunization Logistics and Supply Systems: From Vision to Action. Workshops Report: Washington, DC (July 19, 2010), Seattle, WA (July 22, 2010). Accessed at www.who.int/immunization_delivery/systems_policy/Optimize_Vision-Workshops_Report.pdf.
14. U.S. Department of Health and Human Services. HHS awards contracts to develop new flu vaccine technology. Accessed at www.hhs.gov/news/press/2011pres/02/20110228a.html

Vaccines: A Paradigm Shift



Traditionally used as a preventive measure against a variety of diseases, vaccines are now being used to diagnose immune-deficient patients, and research is being conducted to use vaccines to treat immune and autoimmune diseases.

By Kris McFalls

Vaccines have been used to prevent a host of diseases for hundreds of years. But, more recently, vaccines are being utilized to help evaluate and diagnose patients with primary immunodeficiency disease (PIDD). And, it is hoped that in the future, research that is being conducted will determine how vaccines can be used as a treatment option for immune-deficient and autoimmune diseases.

Vaccines as a Diagnostic Tool

The first pneumococcal vaccine was licensed in 1977. A short time later in 1980, Dr. Gerald Schiffman and colleagues published a paper on the antibody response to pneumococcal vaccines in the *Journal of Immunological Methods*.[1] This led to using vaccines to test a patient's ability to mount a protective antibody response as the standard of care when diagnosing a patient with a suspected immunodeficiency. According to the authors of *Essentials of Clinical Immunology* (5th edition), "Failure to make specific antibody after immunization is fundamental to the diagnosis.… Measurements of IgG subclasses are meaningless unless backed up by test immunizations and detection of specific IgG response."[2]

To determine the level of functional antibodies, a patient's serum levels are measured pre- and post-vaccination. If the serotypes do not reach a protective level after vaccination, the patient could be susceptible to recurrent and opportunistic infections. Therefore, even if the patient has normal immunoglobulin levels, it is important to measure the functionality of the antibodies.

A number of factors should be considered when deciding which vaccine to use when evaluating a patient's functional immunity. Infants, for instance, are not able to formulate a response to all polysaccharide antigens. To compensate, polysaccharides are coupled with peptides to form a conjugated vaccine. Peptides cause helper T cells to be activated and proliferate. In turn, B cells can recognize molecules of the polysaccharide component, which leads to antibody production and formation of memory cells.[3] The memory cells can then be measured to determine if the child is able to formulate a protective response. (See Table 1.)

Therapeutic Vaccines

Historically, immunotherapy using vaccines has widely been viewed as disease prevention, rather than disease treatment. And, although vaccines have been used to diagnose immunological diseases, immunology itself has not played a large role in the development of vaccines. Most successful vaccines have utilized the induction of protective antibodies. Therapeutic vaccines of the future, however, will require the induction of T cell immunity.[4]

Dendritic Cell Vaccines

Dendritic vaccines hold a great deal of hope for cancer patients by using T cells to help destroy cancer cells. Dendritic vaccines are made by extracting the patient's dendritic cells and exposing them to immune stimulants, which in turn reproduces large amounts of dendritic cells. Those cells are then exposed to antigens from the patient's cancer cells and injected back into the patient. The vaccine works by breaking down the antigens on the cell surface into smaller pieces, which allows the antigens to be more visible to the killer T cells that ultimately destroy the cancer cells. Provenge, recently approved for the treatment of prostate cancer, is an example of a dendritic vaccine.[5]

Tumor Cell Vaccines

Tumor cell vaccines also hold hope for cancer patients. Tumor vaccines are made by removing tumor cells, killing them to prevent recurrence, modifying the cells and reintroducing them back into the patient. It is hoped that the patient's own immune system will then attack only the cancer cells, leaving other healthy tissue unharmed. These vaccines can be both allogeneic and autologous.

DNA Vaccines

DNA vaccines hold out promise to treat autoimmune diseases. In 1990, John Wolff and associates discovered that an injection of plasmids produces a protein response in mice[6] that appears to stimulate T cells. As a result, labs can now insert the genes of an antigenic component of a pathogen into plasmids in order to test the effectiveness of vaccines.

DNA vaccines hold out promise to treat autoimmune diseases.

The first human trial of a DNA vaccine used to treat an autoimmune disease was reported in the August 2007 issue of *Annals of Neurology*. Rather than stimulate the immune system as had traditionally been done with vaccines, principal investigator Hideki Garren, MD, PhD, from Stanford University and Bayhill Therapeutics sought to down-regulate an already overactive immune system in patients with relapsing/remitting multiple sclerosis. The study showed that the vaccine was safe and well-tolerated. In addition, the study showed a trend toward the reduction of brain lesions for patients on the active vaccine versus the placebo.[7]

Antigen Vaccines

Antigen-based vaccines incite the immune system to fight against it by creating antibodies. Research is focused on creating vaccines that will take specific antigens from, for instance, a cancer cell, and force the immune system to eradicate it. Eventually, it is hoped that therapeutic vaccines will treat diseases such as Alzheimer's, HIV/AIDS, Crohn's disease and Huntington's disease, as well as many other devastating and costly diseases.

Table 1: Protein and Polysaccharide Antigens

Protein antigens	A protein consists of a string of amino acids, which is folded into a complex structure that contains many different parts that can be recognized by the immune system, the so-called "epitopes." A protein antigen has to be taken up by an APC, such as a macrophage, which cuts it into smaller peptides and presents these to helper-T-lymphocytes. Once the helper-T-lymphocyte recognises the presented peptide, APCs and helper-T-lymphocytes activate each other and T-lymphocytes proliferate. Simultaneously, B-lymphocytes that recognize the presented peptide as well are stimulated to proliferate and differentiate into plasma cells that produce the appropriate antibody in great quantities and memory cells that are able to respond more quickly and more vigorously on a second encounter with the same antigen.
Polysaccharide antigens	Polysaccharide molecules consist of repetitive sugar moieties, and they can be recognized by B-lymphocytes without the intervention of APCs and T-lymphocytes. The sugar moieties bind many SLGs onto the B-lymphocyte membrane at the same time; this 'capping' of SLGs drives the activation and proliferation of the cell, leading to production of the appropriate antibody, but without the formation of memory cells.
Conjugated vaccines	Conjugated vaccines consist of polysaccharides coupled to peptides. The immunological reaction to the peptides ensures helper-T-lymphocytes are activated and proliferate, and their "help" can now be used by B-lymphocytes that recognize the repetitive sugar moieties of the polysaccharide component, leading to adequate antibody production and the formation of memory cells, even in the first year of life.

Source: de Vries, E. Using Vaccines to Diagnose Antibody Deficiencies. *European Pediatrics*, Volume 2, Issue 1. Accessed at www.touchbriefings.com/pdf/3211/vries.pdf.

New Pathways Using Immunotherapy Principles

The concept of immunotherapy also is being studied as a possible treatment method for a rare immunodeficiency. In studies recently published in the *Journal of Clinical Investigation*, it was reported that immunologists have discovered that using an alternative signal pathway significantly improved the function in a 13-year-old boy with Wiskott-Aldrich syndrome (WAS). Mutations in the WAS gene prevent the body from producing the WAS protein. Consequently, the body's ability to use cells such as natural killer (NK) cells is compromised, leaving the patient prone to recurrent infections, cancer and premature death. The only known cure for WAS is a stem cell transplant.

Instead of other more well-known therapeutic pathways of treating disease, such as DNA vaccines, researchers identified and used an alternative pathway to restore the normal immune function. They were able to show that by treating the patient with pharmaceutically produced interleukin-2 (IL-2), the patient's own NK cell cytoxicity matched the level to that of a healthy control subject. In an article published on April 15 by *Science Daily*, Dr. Jordan Orange of Children's Hospital of Philadelphia stated: "Although follow-up studies will be necessary to investigate long-range benefits and test IL-2 in additional patients, the initial results are encouraging. If cytokines can provide clinical benefits with low toxicity, this may represent an important advance and opportunity for all patients with Wiskott-Aldrich syndrome."[8]

Hope for the Future

While the focus on therapeutic vaccines for immune-deficient and autoimmune disease patients represents a paradigm shift by researchers, it appears to be one of rapid acceptance and endless possibilities. Vaccinology has the potential to revolutionize patient treatments, targeting currently incurable diseases and rendering them powerless against the human body. ❖

KRIS MCFALLS *is the patient advocate for* IG Living *magazine and a staff writer for* IG Living *and* BioSupply Trends Quarterly *magazines.*

References

1. Schiffman, G, Douglas, RM, Bonner, MJ, Robbins, M, Austrian, R. A Radioimmunoassay for Immunologic Phenomena in Pneumococcal Disease and for the Antibody Response to Pneumococcal Vaccines. *Journal of Immunology Methods*, 1980;33(2):133-44.
2. Chapel, H, Haeney, M, Misbah, S, Snowden, N. *Essentials of Clinical Immunology*, Blackwell Publishing 2006, p54.
3. de Vries, E. Using Vaccines to Diagnose Antibody Deficiencies. *European Pediatrics*, Volume 2, Issue 1. Accessed at www.touchbriefings.com/pdf/3211/vries.pdf.
4. Plotkin, SA. Vaccines: Past, Present and Future. *Nature Medicine*, 11, S5-S11, 2005. Accessed at www.nature.com/nm/journal/v11/n4s/abs/nm1209.html.
5. WebMD. Treating Diseases with Vaccines. Accessed at www.webmd.com/a-to-z-guides/features/treating-disease-with-vaccines.
6. Wolff, JA, Malone, RW, Williams, P, et al. Direct gene transfer into mouse muscle in vitro. *Science*, 247:1465-1468, 1990.
7. Cassels, C. Autoimmune Disease Vaccine Safe, Potentially Beneficial in MS. *Medscape Today News*. Aug. 15, 2007. Accessed at www.medscape.com/viewarticle/561431.
8. Orange, JS, Roy-Ghanta, S, Mace, EM, Maru, S, Rak, GD, Sanborn, KB, Fasth, A, Saltzman, R, Paisley, A, Monaco-Shawver, L, Banerjee, PP, Pandey, R. IL-2 Induces a WAVE2-Dependent Pathway for Actin Reorganization that Enables WASp-Independent Human NK Cell Function. *Journal of Clinical Investigation*, 2011; 121 (4): 1535 DOI: 10.1172/JCI44862.

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

> Order FLUVIRIN® now and help protect your patients for the 2011-2012 flu season.

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.

Novartis Vaccines is committed to providing seasonal flu vaccine doses on time. In fact, in 2010 Novartis Vaccines completed the shipping of ~40 million seasonal flu vaccine doses ahead of schedule, allowing for early and convenient administration.

> Make sure you have your supply of vaccine ready for the next flu season. Contact FFF Enterprises at (800) 843-7477 or visit www.MyFluVaccine.com

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.

References: 1. Avert. United States HIV & AIDS Statistics Summary. Avert Web site. http://www.avert.org/usa-statistics.htm. Accessed October 27, 2010. **2.** American Cancer Society. Breast Cancer Overview: How Many Women Get Breast Cancer? American Cancer Society Web site. http://www.cancer.org/Cancer/BreastCancer/OverviewGuide/breast-cancer-overview-key-statistics. Accessed November 1, 2010. **3.** Centers for Disease Control and Prevention. Questions & Answers: Seasonal Influenza. CDC Web site. http://www.cdc.gov/flu/about/qa/disease.htm. Accessed October 26, 2010. **4.** Centers for Disease Control and Prevention *(MMWR)*. Prevention and Control of Influenza with Vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. CDC Web site. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr59e0729a1.htm. Accessed November 17, 2010.

NOVARTIS VACCINES

Novartis Vaccines and Diagnostics, Inc.
Cambridge, MA 02139

 Printed in USA February 2011 NVDFLU286-1 Printed on Recycled Paper

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.]*

Manufactured by: Novartis Vaccines and Diagnostics Limited, Speke, Liverpool, UK
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The Value of Vaccines

From the eradication of smallpox to the potential development of a preventive vaccine for AIDS, immunization is a lifesaving innovation that has proven to be the most transformative public health achievement of the 20th century.

By Trudie Mitschang

If an ounce of prevention is worth a pound of cure, then vaccines are truly one of the most transformative public health achievements to come from the 20th century. Since their introduction, vaccines have eradicated smallpox, eliminated wild poliovirus in the United States, and significantly reduced the number of cases of measles and other diseases. Unfortunately, the successful track record of immunizations in the U.S. and other developed countries has led to an unwelcome side effect: Many people no longer understand the value of vaccines because they have never lived in a time when common childhood diseases were almost always deadly. While some may still view vaccines in a favorable light, increasingly vocal opponents regard them with suspicion and even contempt. Within the medical community, the need to educate and advocate on behalf of vaccine awareness, safety and efficacy has never been more urgent.

In a statement made during an April 2009 interview, Dr. David Tayloe, pediatrician and then-president of the American Academy of Pediatrics, stated: "Our citizens need to understand that the vaccine program has been extremely successful. It's the

most effective public health program in the history of man, and we cannot let down our guard just because we've done such a good job. We must continue to protect our children and protect our population."[1]

History of Immunization

Vaccines are a relatively recent development in medical history. It was just more than 200 years ago when English scientist Edward Jenner observed that milkmaids who had been exposed to cowpox seemed immune to contracting the dreaded smallpox infection. In 1796, Jenner tested his hypothesis by inoculating a boy named James Phipps with material from cowpox blisters. He later repeated the experiment on the boy, but this time added a small amount of smallpox, hoping the procedure would immunize James against infection. The experiment was a success, and Jenner's discovery ushered in the dawn of the immunization age.[2]

It would be nearly a century later before the next scientific breakthrough in immunization occurred. In 1885, Dr. Louis Pasteur proved that infecting humans with weakened disease strains could prevent infection. Using an early form of a rabies vaccine, Pasteur successfully immunized a boy named Joseph Meister, who had been bitten by a rabid dog.[3]

By the mid-20th century, steady progress in immunization research had been made. Jonas Salk, MD, and Albert Sabin, MD, developed the inactivated polio vaccine and live polio vaccine, respectively. Their medical discoveries went on to save countless children worldwide from a disease that frequently left its victims wheelchair-bound or dependent on crutches for the rest of their lives. At the height of the polio epidemic in 1952, nearly 60,000 cases with more than 3,000 deaths were reported in the U.S. alone. However, with widespread vaccination, polio occurring through natural infection was eliminated from the U.S. by 1979, and eliminated from the Western Hemisphere by 1991.[4]

A century ago, parents would have expressed disbelief that future generations of families would be able to protect their children from serious childhood infectious diseases. For many of us today, it is difficult to imagine a time when diseases like diphtheria claimed more than 10,000 lives annually in the U.S. Measles, another common disease, infected nearly half a million children in the U.S. each year, often leading to complications such as pneumonia and encephalitis. But, thanks to the advent of immunizations, many of these statistics have taken a positive turn.

Smallpox was declared eradicated from the world in 1977. As stated previously, polio was officially eliminated from the Western Hemisphere in 1991. The numbers for diphtheria are equally impressive: There were 12,230 deaths from diphtheria in the U.S. in 1921 (prior to the availability of a vaccine), but by 1998, just one case of diphtheria was documented. For the most part, the list of serious diseases that have been eradicated, or whose numbers have been dramatically reduced by immunizations, has grown steadily to include mumps, measles, rubella and tetanus.[5] Documenting such data is important, because in the wake of increasing vaccine complacency, many of these once-eradicated diseases have begun making a comeback.[6]

Vaccine-Preventable Diseases on the Rise

According to the World Health Organization (WHO), at least two million people from all age groups die every year from diseases preventable by recommended vaccines. In fact, statistics show that more Americans die each year from vaccine-preventable diseases than from car accidents, breast cancer or AIDS. Influenza, commonly referred to as the flu, is at the root of an estimated 400,000 deaths worldwide each year and, surprisingly, flu-related complications claim more lives than all other vaccine-preventable diseases combined. Another 2.1 million people die each year from diseases for which vaccines have yet to be developed.

In the wake of increasing vaccine complacency, many of these once-eradicated diseases have begun making a comeback.

In undeveloped countries, the statistics are even grimmer. The burden of vaccine-preventable death and disease is daunting; despite significant progress worldwide, two to three million children under age 5 die each year from diseases that could be prevented through immunization.[7]

One of the reasons communicable diseases seem to be rapidly reappearing is due to the global nature of the world in which we live. In many cases, coming into contact with unwanted illness and disease is a mere plane trip away. The California measles outbreak of 2008, for example, began when an unvaccinated child was exposed to measles during a trip to Sweden. He returned and quickly infected friends and classmates. Just how easily these types of infections can spread is documented by other recent outbreaks and epidemics:[8]

• Rates of diphtheria, pertussis and measles greatly increased after the breakup of the Soviet Union as vaccines became less

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

Fluzone® High-Dose
INFLUENZA VIRUS VACCINE

Fluzone High-Dose vaccine:

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

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

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

[c] ACIP=Advisory Committee on Immunization Practices.

Indication

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

Safety Information

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

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

Reserve your doses of Fluzone High-Dose vaccine today.
Log onto VaccineShoppe.com® or call 1-800-VACCINE (1-800-822-2463).

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

References: 1. Fluzone Vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2010. **2.** Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis.* 2009;200:172-180. **3.** Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR.* 2010:59(RR-8);1-62.

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The vaccines division of sanofi-aventis Group

Fluzone® High-Dose Influenza Virus Vaccine

2010-2011 Formula

℞ only

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Dosage and Schedule

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

Table 1: Fluzone High-Dose

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

Administration

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

Adults 65 years of age and older

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

DOSAGE FORMS AND STRENGTHS

Fluzone High-Dose

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

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

Altered Immunocompetence

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

Preventing and Managing Allergic Reactions

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

Limitations of Vaccine Effectiveness

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

ADVERSE REACTIONS

Clinical Trial Experience

Fluzone High-Dose

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Post-Marketing Experience

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

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

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

Other Adverse Events Associated with Influenza Vaccines

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

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

USE IN SPECIFIC POPULATIONS

Fluzone High-Dose

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

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

CLINICAL STUDIES

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

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

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

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

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

Note: As defined in the study protocol:

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

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

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

REFERENCES

1. Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009;58(RR-8):1-52.

2. NCT00391053: www.clinicaltrials.gov.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

Fluzone High-Dose

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

Storage and Handling

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

PATIENT COUNSELING INFORMATION

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

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

Product information as of July 2010.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

Printed in USA

MKT20500-1-1R

5959-60-61

available in Russia and the other newly independent states. Cases of diphtheria reached epidemic levels by 1995, and there were more than 4,000 deaths during the outbreak.

• In 2000, an outbreak of measles in Ireland occurred after routine use of the measles-mumps-rubella (MMR) vaccine fell because of vaccine safety fears. That led to 1,407 cases and admission of 111 children to the hospital; three of those children died.

• In a similar case, incidents of measles in England were up to 740 in 2006 and 971 in 2007 after autism concerns resulted in decreased use of the MMR vaccine.

• In 1992, polio outbreaks were seen in the Netherlands. A similar outbreak had occurred in the U.S. and Canada in 1978. All were among groups of unimmunized people.

• Pertussis outbreaks in Japan (1979) and Sweden (1983) after immunization rates decreased resulted in the deaths of 41 children.

• A rubella epidemic in 1991 among the Amish in Pennsylvania, who had low immunization rates, led to 95 pregnant women getting rubella, nine miscarriages and 11 cases of congenital rubella syndrome.

The American Academy of Pediatrics stated the following in its handout *Vaccine Safety: The Facts*: "Vaccines are necessary.… In many parts of the world many vaccine-preventable diseases are still common. Since diseases may be brought into the United States by Americans who travel abroad or from people visiting areas with current disease outbreaks, it's important that your children are vaccinated."[9]

At least two million people from all age groups die every year from diseases preventable by recommended vaccines.

Vaccine Breakthroughs, From Development to Delivery

Vaccine development has come a long way since Edward Jenner experimentally injected the pus from a cowpox blister into a young patient, leading to the creation of the smallpox vaccine. That first smallpox vaccine consisted of a live attenuated virus that had been weakened enough to provoke an immune response without causing a full-blown infection. Many of today's vaccines, including measles and some influenza vaccines, also use live attenuated viruses, while others use killed forms of viruses, particles of bacteria and inactivated

toxins. Currently, scientists are experimenting with new techniques in vaccine development, including the use of live recombinant vaccines and DNA vaccines.[10]

Live recombinant vaccines use attenuated viruses (or bacterial strains) as vectors: A virus or bacterium from one disease essentially acts as a delivery device for an immunogenic protein from another infectious agent. In some cases, this approach is used to enhance the immune response; in others, it is used when giving the actual agent as a vaccine would cause disease. For example, HIV cannot be attenuated enough to be given as a vaccine in humans; it could cause AIDS.

DNA vaccines consist of DNA coding for a particular antigen, which is directly injected into the muscle. The DNA itself inserts into the individual's cells, which then produce the antigen from the infectious agent. Since this antigen is foreign, it generates an immune response. This type of vaccine has the benefit of being relatively easy to produce, since DNA is very stable and easy to manufacture. However, this technique is still experimental because no DNA-based vaccines have been shown to elicit the substantial immune response required to prevent infection. Researchers are hopeful that DNA vaccines may be able to generate immunity against parasitic diseases such as malaria (currently, there is no human vaccine that is effective against parasites).

The way vaccines are administered also is evolving. When most people think of vaccination, they think of a physician administering a shot. But future delivery methods will expand on that model to offer options with the potential to serve larger segments of the population. One new method showing promise is the use of inhaled vaccines. Influenza nasal sprays already

are being used for seasonal flu, and other options on the horizon may include vaccine patches containing a matrix of tiny needles that deliver a vaccine without the need for a syringe. This method of delivery could be particularly useful in remote areas, as its application would not require administration by a trained physician or nurse.

Breakthroughs in the development of new vaccines have been making headlines lately, but significant improvements to existing vaccines also may be on the horizon.

An analysis of shipping and storage methods also is necessary in the quest to improve global vaccination rates. One of the challenges the industry now faces is known as the "cold chain" problem. Because many vaccines require cool storage temperatures in order to remain viable, their use in areas of the world where temperature-controlled storage is nonexistent is severely limited. Ironically, these tend to be the very parts of the world where vaccination is vitally needed for disease control. That's why the race is on to develop vaccine materials that can be transported in a wide range of conditions without losing their efficacy.

Breakthroughs in the development of new vaccines have been making headlines lately, but significant improvements to existing vaccines also may be on the horizon. In a news release earlier this year, scientists at Oxford University announced they had successfully tested a universal flu vaccine that could work against all known strains of the illness, taking a significant step in the fight against a disease that affects billions of people annually.[11]

According to the study, the treatment targets a different part of the flu virus than traditional vaccines, meaning it does not need expensive reformulation every year to match the most prevalent virus strains that are circulating. Researchers say that if used widely, a universal flu vaccine could prevent pandemics such as the swine flu outbreaks of recent years, and end the need for a seasonal flu vaccine.

In response to the study's findings, Mark Fielder, a medical microbiologist at Kingston University, said: "This study represents some potentially very exciting findings with positive implications not only for influenza but possibly for infectious disease in a wider context. The findings are extremely encouraging in terms of the apparent efficacy of the virus and that it appears to be a safe formulation. However, I think that a larger trial will be able to confirm these findings and let this technology be taken forward."[12]

Future Challenges to the Success of Vaccines

Vaccines have long led the arsenal in our battle against disease. Clearly, many public health achievements can be attributed to immunization, but the future success of the vaccine industry will not hinge on development alone. Challenges in funding, research, storage and distribution are factors as well. Even as the medical world celebrates the successful clinical trials for vaccines to treat diseases like HIV/AIDS, countries most impacted by such epidemics are often too impoverished to afford them. In many of these regions, infrastructures for vaccination are so poor or nonexistent that even currently available vaccines cannot be successfully delivered. Today's medical researchers are tasked with improving the effectiveness of existing vaccines, developing new vaccines, lowering costs and innovating delivery methods to ensure that lifesaving vaccines can reach the population groups that need them most. ❖

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References

1. American Academy of Pediatrics. Sound Advice interview transcription. Accessed at www.aap.org/immunization/multimedia/soundadvice.html.
2. Riedel, S. Edward Jenner and the History of Smallpox and Vaccination. Department of Pathology, Baylor University Medical Center. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC1200696.
3. Encyclopedia of World Biography. Louis Pasteur Biography. Accessed at www.notablebiographies.com/Ni-Pe/Pasteur-Louis.html.
4. Kids Health/Infections: Polio. KidsHealth. Accessed at kidshealth.org/parent/infections/bacterial_viral/polio.html.
5. Trust for America's Health. Closing the Vaccination Gap: A Shot in the Arm for Childhood Immunization Programs, August 2004. Accessed at www.ecbt.org/media/pdf/TFAH_ImmunizationRpt.pdf.
6. Healthy Children. History of Immunizations. Accessed at www.healthychildren.org/English/safety-prevention/immunizations/pages/History-of-Immunizations.aspx.
7. World Health Organization. Vaccine-Preventable Diseases. Accessed at www.who.int/immunization_monitoring/diseases/en/.
8. Iannelli, V. Vaccine Preventable Illnesses. About.com, Dec. 13, 2009. Accessed at pediatrics.about.com/od/immunizations/a/0408_im_illness.htm.
9. American Academy of Pediatrics. Vaccine Safety: The Facts. Accessed at www.aap.org/immunization/families/vaccinesafety_parenthandout.pdf.
10. The History of Vaccines. The Future of Immunization. Accessed at www.historyofvaccines.org/content/articles/future-immunization.
11. Oxford Biomedical Research Centre. Universal Flu Vaccine Developed in Oxford. Accessed at www.oxfordbrc.org/media/news/517/.
12. Before It's News. Universal Flu Vaccine Human Clinical Trials Report Success, Feb. 7, 2011. Accessed at m.beforeitsnews.com/story/401/375/Universal_Flu_Vaccine_human_clinical_trials_reports_success.html.

FAMILIES FIGHTING FLU (FFF) is a nonprofit, 501(c)(3) volunteer-based advocacy organization dedicated to protecting the lives of children by helping to increase annual influenza vaccination rates among families. Our members include families whose children have suffered serious medical complications or died from influenza, as well as health care practitioners and advocates committed to flu prevention.

Share in our mission to protect all children against influenza and save lives.

Visit **www.FamiliesFightingFlu.org** Call **(888) 2ENDFLU** (888-236-3358)

FAMILIES FIGHTING FLU, INC.

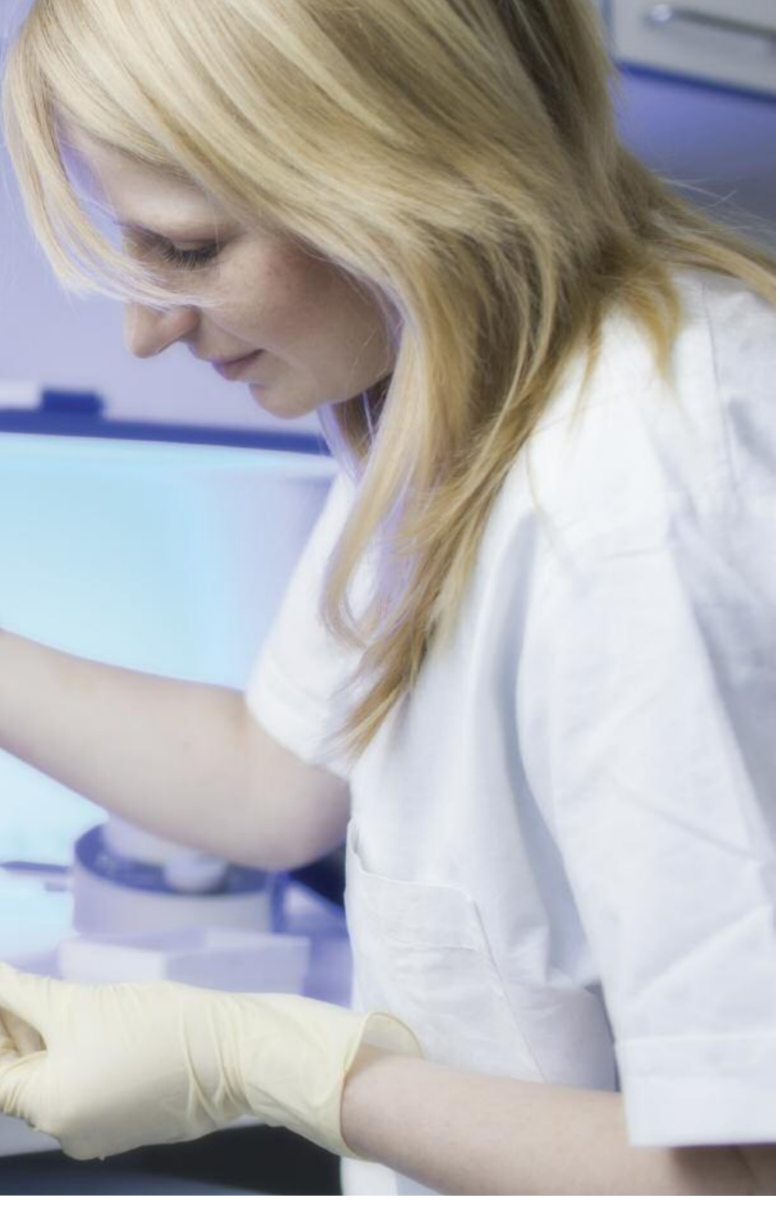
Federal Funding of Vaccine Research

To secure a federal grant, researchers must navigate a rigorous and long application process. But, when completed properly, those projects deemed most likely to have an impact on the nation's health do get funded.

By Amy Scanlin, MS

Since the widespread outbreak of smallpox, there has been continued research and subsequent development worldwide of vaccines to provide protection against a multitude of infectious diseases. In 2006, the World Health Organization's Institute for Vaccine Research identified nearly 200 new vaccines in the research and development stages. And, with innovations in science and identification of new diseases, particularly in the past decade, the public market for vaccines, as well as the quest to provide them, intensifies.

In the U.S., the National Institutes of Health (NIH) has devoted more than $1.6 million to vaccine-related research in the fiscal year 2011 alone, not including funding for HIV/AIDS research. Each fiscal year, Congress provides the NIH's budget for 215 different research areas and, in turn, the NIH provides funding to those research projects that are most urgent to our nation's health. The National Institutes for Allergy and Infectious Diseases (NIAID) is a department of the NIH that supports research in the areas of existing and



emerging infectious, immunologic and allergic diseases. Forecasting two years ahead, NIAID, along with focus groups, looks at which areas of health are worthy of research and development funding. These focus areas are further refined by NIAID staff, looking at relevancy, merit, priority, budget and funding before finalizing, authorizing and making funding announcements for grant applications to the public.

Securing grant funding in the area of vaccine research is a straightforward yet daunting process. And the competition for funding is fierce, as thousands of applications are received yearly.

Searching for Available Funding

The NIH supports two types of research: specialized studies requested through specific funding opportunity announcements (FOAs) and investigator-initiated studies requested through general "parent FOAs," with the majority of the grant budget going to the latter. When considering the types of research to fund, the NIH looks for applications that focus on areas it considers to be most relevant to its mission: to foster innovative research that will prevent disease.

While those interested in grants through the NIH can search the www.grants.gov website, they also can begin their search directly through the NIH and its Institutes and Centers (IC), which are separated by area of research. Each IC lists research priorities and application requests, as well as any specific instructions for applications. Specific instructions found in the FOA supersede any instructions found elsewhere.

In the U.S., the National Institutes of Health (NIH) has devoted more than $1.6 million to vaccine-related research in the fiscal year 2011 alone.

Once a grant opportunity with a good fit to the proposed area of research is identified, it takes approximately three to five days to complete an application, assuming all necessary information is onhand and the requested information is correctly submitted and received by the NIH. Grant administrators (those who submit the grant applications) are encouraged to make contact with an IC program official with any questions prior to submitting an application to ensure their application is complete.

Applying for a Federal Grant

Prior to applying for a grant, registration at both Grants.gov and the Electronic Research Administration (eRA) Commons at https://commons.era.nih.gov/commons is required. Again, this registration process can take days to weeks, depending on the readiness at hand of the required information.

The "Commons," as the eRA Commons is popularly known, is a portal for grant applicants, recipients and NIH extramural grantee organizations to transmit information about the administration of biomedical research. It works in tandem with Grants.gov to process grant applications from the time of submission through monetary award.

Preregistration requirements. Before registering at www.grants.gov, an organizational or personal data universal number system (DUNS) number is required, which provides the Office of Management and Budget better oversight of which organizations receive grant money and

how that money is dispersed. A DUNS number can be obtained at no charge on the Dun and Bradstreet website at http://fedgov.dnb.com/webform.

Once a DUNS number has been obtained, it is necessary to register at the Central Contractor Registration (CCR) office (www.ccr.gov), a registry of vendors doing business with the federal government, for a CCR number. This will require either an IRS employment identification number (EIN) or taxpayer identification number (TIN). Registration should take a matter of business days, unless an EIN or TIN needs to be obtained from the IRS, which can increase the total processing time by as much as a few weeks.

After obtaining the DUNS and CCR numbers, registration for an application at www.grants.gov is possible. Then, after registration is completed and approved, and the grant opportunity has been identified, the application package is available for download and may, in turn, be electronically submitted when complete.

Funding eligibility. Each grant has its own eligibility requirements. In general, nonprofits, which include state and local governments, educational research institutions and Indian tribal governments and organizations, are eligible. In some cases, for-profit organizations are not authorized to apply for a grant, and in other cases, for-profits may be permitted, but they may not profit from federal cooperative agreement funds.

Research projects that will use human subjects must follow additional steps to meet Health and Human Services (HHS) requirements for the protection, safety and ethical treatment of the study participants. First, they must obtain an assurance number from the Office of Human Research Protection (OHRP) in accordance with the Code for Federal Regulations, Title 45, Part 46, which protects human subjects. While there are four types of assurances, the OHRP suggests registering for a Federalwide Assurance because it is the easiest to complete and covers the broadest range of studies. A registration form and instructions for applying for an assurance can be accessed at www.washington.edu/research/hsd/topics/Federalwide+Assurance+(FWA).

When considering the types of research to fund, the NIH looks for applications that focus on areas it considers to be most relevant to its mission.

Applicants also must register with the Institutional Review Board (IRB) that has agreed to review research in their area of study. The NIAID recommends consulting the IRB first before making a determination to use human subjects. If it is determined that human subjects will not be used, an explanation needs to be provided for each project involved in the research.

It's important to note that the NIH offers FOAs tailored to new investigators, such as the NIH Director's New Innovator Award. So, filing for an application under the new researcher's name rather than under an established organization's name may help. New applicants are given greater consideration by reviewers of their proposals, more so than organizations that have a research track record for which the new applicant works. However, new investigators must prove they have resources for the study, institutional support and the ability to lead the investigation.

Application process. It can take as long as 10 months from the time an application is submitted to receive notification of an award, so it is important to plan early. Exceptions to this timetable are grants for AIDS research funding, which have an expedited review process.

The application should be viewable in the Commons before

it is finalized. If the grant administrator submitting the packet is unable to view it, NIH will not be able to view it either.

Once an application is confirmed to be compliant with NIH policies, as well as with federal research policies, the application is referred to the Division of Receipt and Referral in the Center of Scientific Review (CSR) which will, in turn, assign it to an IC and a Scientific Review Group (SRG) for it to assign reviewers for consideration.

Generally, there are three funding cycles yearly, and it can take at least six months from the start of the initial review to a start date for the research. For example, in cycle one, the application due date is between February and March, depending on the specific area of the application. The Scientific Merit Review will take place between June and July, and the Advisory Council will meet roughly in August or October, with an earliest projected start date, once funding has been approved, between September and December.

Applicants should also take note of when the application is due. If submitting by mail, some FOAs require an application be postmarked by a certain date, while others require the application be received by a certain date.

Application evaluation. Grant applications to the NIH are evaluated in a multi-step, dual peer-review process in accordance with section 492 of the Public Health Service Act and federal regulations governing "Scientific Peer Review of Research Grant Applications and Research and Development Contract Projects."

SRG scientists who have a specialty in the area of the grant will evaluate the application based on the criteria in the FOA. The IC National Advisory Councils or Boards also will evaluate the application.

Review process. SRG reviewers will provide a priority or impact score, which addresses the projected impact of the research on the long-term influence of the field involved. They will ask questions such as:

- Will the research address a particular problem in the field, and if so, how will the field be impacted?
- Are those involved in the study qualified and well-suited to the subject?
- Will the research address the problem in a new way with innovative methodologies or concepts?
- Is the methodology to be used appropriate to the question at hand?
- Will the work of the study be done in an environment that will promote success?

Reviewers also will be looking at the ethics of the study, the safety of study participants, any biohazards, etc. The application does not need to be strong in each area to receive a favorable review. Prior to peer group meetings, each individual reviewer will provide a priority score for each criteria, as well as a summary statement, both available to the applicant via the Commons whether or not the proposal moves forward in the process. The reviewers also will provide an overall impact score based on the criteria, which will decide which applications go forward for further review.

It can take as long as 10 months from the time an application is submitted to receive notification of an award, so it is important to plan early.

Then, the IC council reviews the application, impact scores and summary statements for each application against its needs. The IC director makes final funding decisions based on the council's information. Both SRGs and IC peer groups must recommend the proposed study for it to be approved.

Notification

Should the application be funded, the IC will send a Notice of Award, and the IC will work closely with the applicant on the administration of the program. Should an application for funding be denied, the NIH offers resources and processes for resubmission, unless the grant application is for a specific initiative with specific money set aside for it.

The Funding Is There

With proper planning, an eye for detail, procedure and organization, obtaining a federal grant is just a few mouse clicks and several months away. The keys to being awarded a grant are to 1) make sure the area of study is not only in a high-priority area, but that it specifically addresses those areas of need; 2) prepare for the application by obtaining necessary registrations; and 3) pay close attention to detail when submitting the application. The NIH and specific ICs are available to help. It is, after all, their hope to fund research that leads to the next breakthrough in protecting our nation's health. ❖

AMY SCANLIN, MS, *is a freelance writer specializing in medical and fitness writing.*

IVIG

THE EVOLUTION OF THE MANUFACTURING PROCESS

Modifications in the steps and ingredients of the manufacturing process of immune globulin have changed the world of immune therapy.

Talecris Biotherapeutics' manufacturing plant, Clayton, N.C.

By Jerry Siegel, PharmD, FASHP

The process of isolating "gamma" globulins from blood dates back to the 1940s when Cohn and Oncley were able to use a method of cold ethanol fractionation to separate plasma from precipitated antihemophilic factors and use cold ethanol in a secondary step to isolate the "gamma" globulins. The resulting product was crude by today's standards.

The original purpose of the Cohn-Oncley plasma fractionation process (Table 1) was to separate albumin from plasma. The motivation was to supply a plasma "expander" for soldiers in World War II. The shortage of the blood supply could be supplemented with albumin and led to better healing rates in blood-loss-related trauma. The original standard immune globulin (IG) also was used to boost the immune system when

a patient was exposed to certain viruses such as hepatitis A and rubella, as well as for blood clotting and to treat primary immune deficiency disease (PIDD) patients.

These latter byproducts of the fractionation process (antihemophilic factors, fibrin clotting factors and IG clotting factors and IG), however, were considered secondary products, and little research was done to "purify" these products compared with the research conducted to increase the yield and safety of albumin. One modification by Kistler and Nitschmann (Table 2) that was intended to purify albumin used a lower ethanol concentration precipitate A (equivalent to Cohn Fraction II and III). With this, there also was a higher extraction and utilization of 40% ethanol at a lower pH for precipitate B and C, which improved the yield and purity of the end product of albumin.

Table 1: The original Cohn Plasma Fractionation Process

Fraction	FI	FII	FIII	FIV	FV
Ethanol (%)	8	25	18	40	40
pH	7.2	6.9	5.2	5.8	4.8
Temp (°C)	-3	-5	-5	-5	-5
Protein fraction (%)	5.1	3	3	3	1
Products	fibrinogen	globulins	globulins	alpha-1 proteinase; PPF	albumin

Table 2: Kistler and Nitschmann Fractionation Process

Precipitate	A (Cohn FII and FIII)	B (Cohn FIV)	C (Cohn FV)
Ethanol (%)	19	40	40
pH	5.85	5.85	4.8
Temp (°C)	-3	-8	-8
Product	gamma globulins	precipitant discarded	albumin

At this time during the fractionation process, the gamma globulins that were isolated were mixed with numerous proteins other than monomeric IgG to the extent of more than 10%. This posed a problem for PIDD patients. The biggest issue was that these IGs, when administered intravenously, would aggregate, forming what would be perceived as a foreign antigen, resulting in a significant adverse reaction that was anaphylactoid in nature due to activation of complement, which put a patient at risk. Therefore, IG could safely be administered to a PIDD patient only by intramuscular or subcutaneous routes. The tissue would act as a filter to prevent the aggregates from crossing into the bloodstream and prevent a systemic reaction. Yet, local reactions were common with pronounced inflammation, swelling and pain. The maximum dose also was limited by these routes, which limited the overall increase in IgG level. A dose of 60 ml of a 5% product would require six to 12 injections at one time to provide only 3 grams of IgG. And, this dose was very low and inadequate to afford protection from infection.

The primary effort to improve the yield and safety of albumin may account for the nearly 40-year gap between the original fractionation process and the commercial availability of the first intravenous IG (IVIG). In order to prevent these adverse reactions, the immune serum globulin (ISG) needed to be stabilized from aggregation, and purification of the end product to monomeric IgG was necessary. The eventual development of a safe IVIG formulation enabled PIDD patients to receive therapeutic doses of IgG and marked an incredible change in their quality of life. To understand how this came about, it is necessary to understand the evolution of IVIG products and the rationale for each ingredient to improve the product by improving the process.

First-Generation IVIG Products (Figure 1)

While most of the products mentioned here are available in the United States, many have origins outside the U.S. The first IVIG product available in the U.S. was Gamimune produced by Cutter Laboratories. This first commercially available IVIG was a product of reduction and alkylation, which cleaved the disulfide bridges holding the Fc component of the IgG molecule to the Fab (fragment antigen binding) arms. Even though there was biological activity in prevention of infection and protection for these PIDD patients, it did not provide any immunomodulation effects. Gamimune was a 5% solution stabilized in liquid form with maltose, and refrigeration was required for storage.

The second IVIG in the U.S. market, Sandoglobulin (Sandoz) also was the first "intact" IgG preparation. The Kistler-Nitschmann fractionation process was further modified with an extraction at low pH (4.2) and stabilization with sucrose. This carbohydrate stabilizer was selected to prevent an increase in the glycemic index for diabetic patients. This product is lyophilized and required reconstitution with normal saline. The osmolality of a 3% solution was 498 mOsm/kg,

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION PRIOR TO USE

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

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

WARNINGS

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

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

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

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

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

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

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

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

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

Hyperproteinemia, increased serum viscosity, and hyponatremia
Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV therapy. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Gammaplex at the minimum rate of infusion practicable.

Thrombotic events
Thrombotic events may occur following treatment with IGIV products. Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), hyperproteinemia or monoclonal gammopathies (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests). For patients judged to be at risk of developing thrombotic events, administer Gammaplex at the minimum rate of infusion possible.

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

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

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

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

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

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

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

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

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

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

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

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

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

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Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

Positive efficacy outcomes
For PI patients receiving Gammaplex there were:

> No reports of Acute Serious Bacterial Infection[1]
> Just 0.75 days per year of subjects hospitalized[1]
> Only 8.73 days per subject year out of work/school/day care[1]

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

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

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

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

For more information visit **www.gammaplex.com**

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

WARNING: Renal dysfunction, acute renal failure, osmotic nephropathy and death may be associated with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gammaplex does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable. See full prescribing information for complete boxed warning.

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

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

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

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

In clinical studies, the most common adverse reactions with Gammaplex were headache, fatigue, nausea, pyrexia, hypertension, myalgia, pain and vomiting.

Report adverse reactions to adr@bpl.co.uk

REFERENCES
1. BPL. US Prescribing Information, VSUS1PI, Sept. 2009.

For product information & inquiries, call: **(772) 453-9084**

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Please see the Brief Summary of Prescribing Information, including boxed warning, on the previous page.

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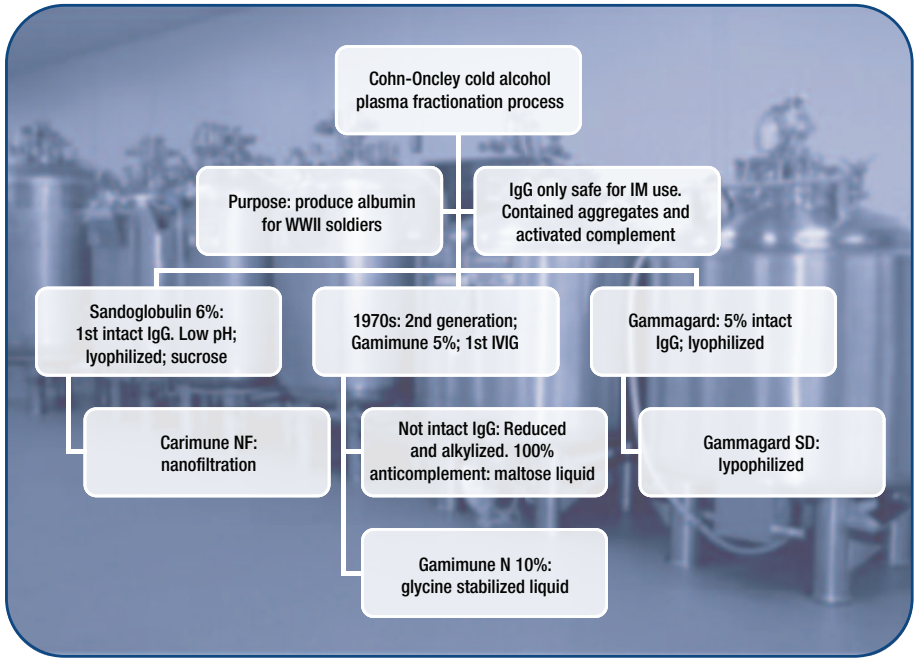
Figure 1.



while the 6% solution was 690 mOsm/kg and the 12% was 1074 mOsm/kg. These hypertonic solutions create a solution that is hyperviscous and can increase risk of renal insufficiency and thromboembolic adverse events. Even though this product contained the IgG subclass distribution in a close proximity of normal serum, its IgA content was approximately 720 mcg/ml. For patients who had an IgA-specific deficiency, there was concern that an anaphylactic reaction could occur if this product was administered. Yet, while the occurrence of having an IgA deficiency that was mediated by an anti-IgA (IgE or IgG) antibody was extremely rare, it still concerned physicians.

The third product that would still be classified as a first-generation IVIG was Gammagard (Baxter). This product also was lyophilized, but it used glucose as the stabilizer. The plasma fractionation method was Cohn-Oncley, but it also employed anion exchange chromatography for purification. The main focus of this product was to provide a low-IgA product. However, in doing so, the IgG3 and IgG4 subclasses were lower than seen in Sandoglobulin. Another European product, IVeegam, also was a low-IgA product, but it had no IgG3 subclass in the final product. For passive immunization, it was presumed that all four subclasses should be represented in the proportions seen in human serum. This theory was based on the observation that IgG1 and IgG3 worked as pairs as do IgG2 and IgG4.

With the entry of two IVIG "intact" products on the market, Gamimune was reformulated without using reduction/alkylation methods to provide the third "intact" IVIG. Gamimune N also was stabilized in glycine, but it did not contain maltose. It was stable at pH 4.2 as a liquid product that required refrigeration for stability. This product also contained no sodium chloride and had a relatively lower osmolality than the other two products.

pH Incubation

Fractionation methods that employed low pH would not only isolate the IgG monomers but also provide an antimicrobial effect. The lyophilized products would be reconstituted in either normal saline or sterile water, and the final pH of the solution for administration was in a normal range of 6.8 to 7.2. The liquid products would stay in solution in pH ranges of 4.2 to 5.5, a lower pH that was necessary to keep the IgG in a predominantly monomeric form. The lower pH did not induce metabolic acidosis in adults because it was a buffered solution, but caution in neonates had to be observed. In addition to this concern, administration of low pH IVIG in small peripheral veins could cause irritation and phlebitis. The use of catheters eliminated this concern.

The carbohydrate acts to prevent aggregation of the IgG molecules.

Carbohydrate Stabilizers

The carbohydrate acts to prevent aggregation of the IgG molecules. The first IgG stabilizer was maltose. As a complex sugar, maltose does not change the glycemic index for diabetic patients and, therefore, does not need to be covered by insulin. However, some glucose monitors do not distinguish the difference between maltose and glucose and can lead to serious false-positive readings. This problem has led to serious adverse reactions when insulin is administered to a hypoglycemic with a false reading.

Sucrose was the next stabilizer used for IVIG. Like maltose,

1st-Generation IVIG

Product	Manufacturer	Cold Ethanol Fractionation	Anion Exchange Chromotography	Enzymatic Treatment	Low pH Incubation	Ultra Filtration	Nano Filtration	S/D	Octanoic Acid	Pasteurization	Stabilizer	Other
Gamimune 5%	Cutter	Cohn-Oncley			X						maltose	reduction/ alkylation
Sandoglobulin 3-12%	Sandoz	Kistler-Nitschmann		pepsin	X						sucrose	
Gammagard 5%	Baxter	Cohn-Oncley	X								glucose	
Iveegam 5%	Baxter	Cohn-Oncley	X	trypsin							glucose	PEG

2nd-Generation IVIG

Product	Manufacturer	Cold Ethanol Fractionation	Anion Exchange Chromotography	Enzymatic Treatment	Low pH Incubation	Ultra Filtration	Nano Filtration	S/D	Octanoic Acid	Pasteurization	Stabilizer	Other
Gammagard S/D 5%	Baxter	Cohn-Oncley	X					X			glucose	
Gammar P 5%	Armour/ Behring	Cohn-Oncley								X		
Carimune	ZLB Behring	Kistler-Nitschmann		pepsin	X						sucrose	
Octagam 5%	Octapharma	Cohn-Oncley	X			X		X			maltose	
Gamimune N 10%	Miles	Cohn-Oncley			X	X		X			glycine	
Venoglobulin 5%	Alpha Therapeutics	Cohn-Oncley			X	X		X			sorbitol	PEG

it does not require insulin coverage. Even though the concentration of sucrose is listed as 5%, that is only true when the IVIG concentration is 3%. Normally, Sandoglobulin was administered as a 6% solution and, therefore, the sucrose concentration was 10%. At that concentration, the product was hyperosmolar. Increasing reports of renal insufficiency and renal failure were associated with sucrose-stabilized products.

Glucose also is used as a stabilizer. For diabetic patients, the impact on the glycemic index needs to be accounted for and adjusted during administration.

Viral Risk for First-Generation Products

In the 1950s, the Cohn method was an open-vessel production that would not be considered sterile, and it was not pasteurized until the 1960s. The cold ethanol treatment did provide a method of protection from microbial contamination. The strongest evidence for this statement was that there were no cases of HIV transmission through the use of IVIG during the 1980s, when HIV had been transmitted through plasma products and antihemophilic factor products. These products later were heat-treated to prevent transmission of HIV.

In the mid 1990s, there were reports of hepatitis C being transmitted through IVIG products, but they were the ones that used anion exchange chromatography as a method to purify products rather than low pH. These products were recalled and reformulated by using solvent-detergent (S/D) to prevent the transmission of lipid-coated viruses such as hepatitis C. Because S/D does not affect non-lipid-coated viruses

3rd-Generation IVIG

Product	Manufacturer	Cold Ethanol Fractionation	Anion Exchange Chromotography	Enzymatic Treatment	Low pH Incubation	Ultra Filtration	Nano Filtration	S/D	Octanoic Acid	Pasteurization	Stabilizer	Other
Carimune NF	CSL Behring	Kistler-Nitschmann		pepsin	X		X				sucrose	
Flebogamma 5%	Grifols	Cohn-Oncley	X					X		X	sorbitol	
Gamunex 10%	Talecris	Cohn-Oncley	X		X				X		glycine	
Gammaplex 5%	Bio Products Labs	Cohn-Oncley	X		X			X			sorbitol/glycine	

4th-Generation IVIG

Product	Manufacturer	Cold Ethanol Fractionation	Anion Exchange Chromotography	Enzymatic Treatment	Low pH Incubation	Ultra Filtration	Nano Filtration	S/D	Octanoic Acid	Pasteurization	Stabilizer	Other
Privigen 10%	CSL Behring	Cold ethanol	X		X	X	X		X		L-proline	
Gammagard Liquid 10%	Baxter	Cohn-Oncley	X			X		X			glycine	
Gamunex-C 10%	Talecris	Cold ethanol	X		X				X		glycine	
Flebogamma DIF 5%/10%	Grifols	Cohn-Oncley	X		X		X 35+20	X		X	sorbitol	PEG

such as hepatitis A or parvovirus, other antiviral steps needed to be considered.

Second-Generation IVIG Products

The focus of the second-generation products was to eliminate the risk of viral or even prion transmission from IVIG products. The risk-reduction strategy looked at sequential steps that would remove, partition or destroy the virus. Keeping in mind that new viruses and viral mutations can and do occur, the use of methods with different mechanisms would make the process more robust.

All of the current products use either the Cohn-Oncley or Kistler-Nitschmann method for plasma fractionation. The cold ethanol process itself does provide some measure of viral protection. Low pH or incubation at pH 4 to 4.2 also will have an additive impact on antiviral methods. This method increased the efficiency of the process and reduced product protein loss. Anion exchange chromatography is employed to target the extraction of the IgG subclasses and remove IgA, but it also serves to partition the viruses from the protein. This method alone, however, is not sufficient to prevent all viral transmission.

The second-generation products often indicated a viral safety methodology in their brand name such as Gammagard S/D and Gamimune N S/D. Sandoglobulin, which changed its name to ZLB-globulin and now Carimune, was a second-generation product, but it did not employ the use of solvent detergent. This product was never implicated in hepatitis C transmission, and the company felt that its method of low pH incubation and trace enzymatic (pepsin) treatment was sufficient for currently known viral risks.

Third-Generation IVIG Products

When it was determined that humans could be exposed to Creutzfeldt-Jakob disease (CJD) by ingesting meat from cows, with the scare of mad cow disease, there was great concern that blood donors with CJD could expose this risk to recipients of fractionated blood products. Better methods of screening incubation and PCR (polymerase chain

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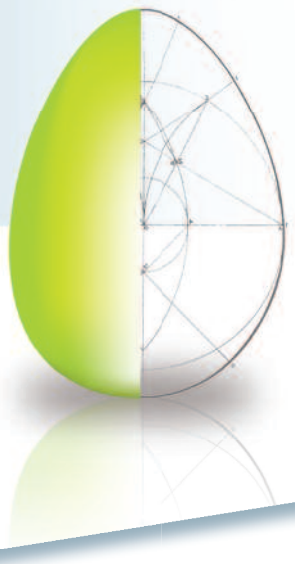
- Sucrose-free
- IgA ≤25 mcg/mL

Safe.

- 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.

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

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

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

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

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

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

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

1 INDICATIONS AND USAGE

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

1.1 Primary Humoral Immunodeficiency

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

1.2 Chronic Immune Thrombocytopenic Purpura

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

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

5.2 Renal Failure

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

5.3 Hyperproteinemia

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

5.4 Thrombotic Events

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

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

5.5 Aseptic Meningitis Syndrome (AMS)

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

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

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

5.6 Hemolysis

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

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

5.7 Transfusion-Related Acute Lung Injury (TRALI)

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

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

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

5.8 Volume Overload

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

5.9 Transmissible Infectious Agents

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

5.10 Monitoring: Laboratory Tests

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

5.11 Interference With Laboratory Tests

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Treatment of Primary Humoral Immunodeficiency

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

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

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

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

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

*Excluding infections.

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

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

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

* Two consecutive daily infusions.

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

6.2 Postmarketing Experience

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

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

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

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Use of Privigen in nursing mothers has not been evaluated.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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reaction) testing were employed on the blood or plasma collection side, but there needed to be a way to ensure that TSE (transmittable spongiform encephalopathy agent) would not contaminate the IVIG products. There was equal concern about new viruses such as West Nile and the risk of transmission.

Gamimune N was replaced with Gamunex (IVIG-C) when caprylate (octanoic acid) was used to replace solvent detergent. The advantage of caprylate was that it was a natural plant (8 chain fatty acid) that did not have to be completely removed (as opposed to S/D) and it was more effective in a shorter time frame. These changes allowed for a more efficient recovery of highly purified (>98%) IgG. This was the first product to use caprylate in its process.

The next step was the introduction of nanofiltration. Many products go through an ultrafiltration process that removes non-IgG proteins and some larger viruses, but the introduction of nanofiltration was adopted to make Carimune NF. It was essentially the same product as Carimune but with the additional nanofiltration step. It also was the first product to have an approved TSE removal step.

Another concern was the risk of renal failure induced by IVIG. IVIG-associated acute renal failure was first reported in 1987. The U.S. Food and Drug Administration (FDA) received more than 114 reports worldwide (87 in the U.S.) of acute renal failure associated with the administration of various IVIG products. The vast majority of these were related to products that were stabilized with sucrose, but there also were occurrences with other carbohydrate-based stabilizers such as glucose and maltose. The patient risk factors included those older than age 60, diabetes mellitus, sepsis, proteinuria, renal insufficiency and concomitant renal risk medications. A black-box warning was issued by the FDA for all IVIG products to warn of such risk.

The first IVIG product available in the U.S. was Gamimune produced by Cutter Laboratories.

As the doses of IVIG continued to increase for the treatment of autoimmune diseases, another risk was discovered. The risk of thromboembolism, including myocardial infarction (MI), was reported in the literature, but the cause was not apparent. It is believed that a combination of risks, including former embolic events and age in combination with the administration of hyperosmolar and hyperviscous solutions administered at a rapid rate, could result in thromboembolism. The immediate recommendation was to use lower concentrations at slower rates, but the concentration of the protein may not be reflective of the osmolality of the solution.

The bottling area at Talecris Biotherapeutics' manufacturing plant

Fourth-Generation IVIG Products

It may be debatable whether or not there is a fourth generation, but the distinction is the movement away from carbohydrate-stabilized IVIG products to those that are in liquid form and amino-acid stabilized. Glycine was used in the very first IVIG product (Gamimune) and is still used today in Gammagard Liquid and Gamunex, both 10% liquid products. The latest amino acid stabilizer is L-proline, which is used in Privigen 10% Liquid. L-proline provides a strong hydrophobic environment to increase monomeric IgG. The theoretical advantage of this amino acid would be in the reduction of routine adverse events such as fever, chills and flushing, and headaches. The new liquid products that are at a

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10% concentration do not contain sugars and only a trace amount of sodium and, thus, have much lower osmolality than their earlier-generation products. These changes are intended to minimize both the renal and thromboembolic risk associated with IVIG administration.

Conclusions

Between 1940 and 1980, very few changes in the manufacturing process left ISGs as products of minimal impact for passive immunization for patients. It was not until the use of additional steps, which included purifying globulin fraction and preventing aggregation to allow IV administration, that the world of immune therapy changed.

An ideal agent would be one that could be administered in a relatively short time (less than one hour) and that does not cause the usual headache, fever, chills and malaise commonly associated with administration of IVIG.

The continuous process of improving the manufacturing process has led to products that are virtually free of microbial risk. As the majority of use has evolved from passive protection for patients with immune deficiency diseases to patients with autoimmune diseases, additional adverse events have developed. Most likely due to administering higher doses at faster rates, such issues as renal failure and thromboembolic risks surfaced. The response to these issues resulted in products that are stabilized with amino acids instead of carbohydrates, resulting in products with a higher concentration that are still iso-osmolar.

What are the next steps to develop the ideal IVIG? A single process that would eliminate the risk of all viruses, prions or future microbial mutations would be ideal. While the current IVIG products are virtually free of risk or microbial transmission, they require multiple and expensive steps to achieve that.

If a higher-concentration IVIG product could be achieved without causing a hyperosmolar product, that would be desirable. The highest concentration of IVIG is currently 10%, which still requires a high volume for administration. The complete elimination of IgA without removing the IgG subclasses would eliminate any concern for anaphylaxis. Even though the risk related to this phenomenon is very rare, it still does exist.

An ideal agent would be one that can be administered in a relatively short time (less than one hour) and that does not cause the usual headache, fever, chills and malaise commonly associated with administration of IVIG. The vast majority of the adverse events related to IVIG are mild and infusion-related. And, the degree of tolerability to treatment depends on the product profile. But, each patient has different degrees of tolerability, and slower infusion rates are often necessary.

Finally, development of an IVIG in its final form ready for administration in common final dosage sizes would be ideal. Currently, since the doses of IVIG usually range from 0.4 to 1.0 grams/kg, the dose exceeds the content of one vial. The largest vial size currently is 20 grams; therefore, either administering sequential vials or pooling the vials into a separate product container is necessary. And, the risk of contamination, error and waste are associated with this common practice. ❖

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References

1. Siegel, J. Intravenous Immune Globulins: Therapeutic, Pharmaceutical and Cost Considerations. *Pharmacy Practice News*, January 2011.
2. Ochs, H, Siegel, J. Stabilizers Used in Intravenous Immunoglobulin Products: A Comparative Review. *Pharmacy Practice News*, July 2010.
3. Wahn, V, Orange, J. *Immunomodulation with Immunoglobulins*. Chapter 8: Clinical Use of Immunoglobulins. UNI-MED Verlag AG Bremen, January 2009.
4. Siegel, J. Avoiding Adverse Events with IVIG. *Pharmacy Purchasing and Products*, February 2010.
5. Siegel, J. Safety Considerations in IGIV Utilization. *International Immunopharmacology*, Vol. 6, Iss. 4, April 2006, pp523-5276.
6. Siegel, J. The Product: All Intravenous Immunoglobulins Are Not Equivalent. *Pharmacotherapy*, 2005 Nov; 25(11 Pt 2):78S-84S.
7. McCue, JP, Hein, Rh, Tenold, R. Three Generations of Immunoglobulin G Preparations for Clinical Use. *Review of Infectious Diseases*, 1986 Jul-Aug; 8 Suppl 4:S374-81.
8. Lebing, W, Remington, KM, Schreiner, C, Paul, HI. Properties of a New Intravenous Immunoglobulin (IGIV-C, 10%) Produced by Virus Inactivation with Caprylate and Column Chromatography. *Vox Sanguinis*, 2003 Apr; 84(3):193-201.
9. Gelfand, EW. Differences Between IGIV Products: Impact on Clinical Outcome. *International Immunopharmacology*, 2006 Apr; 6(4) 592-9.
10. Kempf, C, Stucki, M, Boschetti, N. Pathogen Inactivation and Removal Procedures Used in the Production of Intravenous Immunoglobulins. *Biologicals*, 2007 Mar; 35(1):35-42.
11. Deiz, JM, Cabellero, S, Belda, F, et al. Capacity of the Manufacturing Process of Flebogamma DIF, a New Human High Purity Intravenous Immunoglobulin, to Remove a TSE Model Agent. *Biologicals*, 2010 Nov; 38(6):670-4.

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**.

References: 1. Huth-Kühne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. 2009;94(4):566-575. **2.** Collins PW, Hirsch S, Baglin TP, et al; for UK Haemophilia Centre Doctors' Organisation. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;109(5):1870-1877. **3.** Collins PW, Percy CL. Advances in the understanding of acquired haemophilia A: implications for clinical practice. *Br J Haematol*. 2010;148(2):183-194. **4.** Bitting RL, Bent S, Li Y, Kohlwes J. The prognosis and treatment of acquired hemophilia: a systematic review and meta-analysis. *Blood Coagul Fibrinolysis*. 2009;20(7):517-523.

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Myths and Facts: Antibiotics

Misconceptions about antibiotics, once known as "miracle drugs," result in their misuse and overuse, which has become a worldwide health problem.

By Ronale Tucker Rhodes, MS

The discovery of antibiotics is one of the biggest successes of modern medicine, and they are among the most frequently prescribed medications.[1] The first antibiotic, penicillin, was discovered accidentally in a mold culture in 1928 by bacteriologist Alexander Fleming. And, while he noted it might someday have therapeutic value, penicillin wasn't used until the 1940s when pathologist Howard Florey and chemist Ernst Chain isolated the active ingredient and developed a powdery form of the medicine. Also in the 1940s and 1950s, biochemist and microbiologist Selman Waksman, who coined the term "antibiotics" in 1942 and is now known as the father of antibiotics, isolated a number of other new antibiotics, including streptomycin, chloramphenicol and tetracycline.[2] Today, there are more than 100 different antibiotics available to doctors to cure both minor discomforts, as well as life-threatening infections.[1] But there are many misconceptions behind these once-called "miracle drugs."

Separating Myth from Fact

Myth: Antibiotics can cure almost all illnesses, including the common cold.

Fact: Antibiotics only work to treat bacterial infections. They are useless to treat viral (e.g., colds) or fungal (e.g., ringworm) infections.[1] While some fungi and parasites may be susceptible to certain antibiotics, there are antifungals and antiparasitic agents for their treatment.[3]

Myth: All types of antibiotics are pretty much the same.

Fact: All antibiotics are not equal. There are seven main classes of antibiotics, which comprise more than 100 antibiotics, most of which have two names: a trade or brand name created by the drug company that manufactures the drug, and a generic name based on the antibiotic's chemical structure or chemical class.

Which type of antibiotic an individual needs depends upon many factors. However, the main factor is whether the type

best combats the kind of bacteria causing the infection. For instance, only certain antibiotics will kill bacteria that cause ear infections. Other factors include medication cost, dosing schedule, common side effects, as well as allergic reactions. If a person has allergies, an entire class of antibiotics may have to be eliminated from consideration.

While the type of antibiotic needed is usually determined by a doctor, lab tests and cultures also may help to narrow down which species of bacteria is causing the infection.[1]

Myth: It's easy for doctors to diagnose when an illness requires treatment with antibiotics.

Fact: A bacterial infection is often difficult to diagnose, but there are some common signs that may be indicative of a bacterial infection. For instance, pneumonia may be detected by a persistent cough, stomachache or difficulty breathing. And, sepsis (bacteria in the blood) and bacterial meningitis (bacterial infection in the lining of the brain and spinal cord) may present with a stiff neck or changes in mental status.

There are some symptoms of a bacterial infection that occur as a result of a secondary infection. These include symptoms persisting longer than the expected 10 to 14 days a virus tends to last; a fever higher than one might typically expect from a virus; and a fever that gets worse a few days into the illness rather than improving. Sinusitis, ear infections and pneumonias are common examples of secondary infections.

Other than these, it is difficult to determine if an infection is bacterial without conducting tests. Tests that are frequently performed to diagnose a bacterial infection include a complete blood count and fluid cultures, such as a blood culture, urine culture or spinal culture (which requires a spinal tap).[4]

Myth: Antibiotics can be taken as a preventive measure to protect against some infections.

Fact: There are rare circumstances when antibiotic prophylaxis is recommended, such as pneumocystis pneumonia prophylaxis in HIV patients and during dental and gastrointestinal procedures, when some patients could develop an invasive infection of the heart valves called subacute bacterial endocarditis (SBE). These patients include those who have implanted mechanical or tissue heart valves, abnormal heart valves, a congenital heart defect, Dacron or Teflon vascular grafts or patches over cardiac defects, mitral valve prolapse (only if there is significant leakage) and pacemakers.[5] However, the American Heart Association recently changed its guidelines regarding which patients should take a precautionary antibiotic to prevent infection. This change was in response to a growing body of scientific evidence that shows, for most people, the risks of taking prophylaxis antibiotics for certain procedures outweigh the benefits. These guidelines also are endorsed by the American Dental Association.[6]

Myth: There are few, if any, side effects from antibiotics.

Fact: Antibiotics frequently have side effects. Some of the more common are soft stools or diarrhea and a mild upset stomach. Others that a doctor should be notified about include vomiting, severe watery diarrhea and abdominal cramps, vaginal itching or discharge and white patches on the tongue.[1]

Myth: Many people are allergic to antibiotics.

Fact: Some people are allergic to antibiotics, most commonly penicillin. In fact, about 10 percent of people report having an allergy to penicillin. However, most people who believe they are allergic can take penicillin without a problem, either because they wrongly identified a side effect as an allergy, meaning they were never truly allergic, or their allergy resolved over time.

Distinguishing between nonallergic reactions and true allergic reactions is important. Those who are allergic are typically treated with a less effective or more toxic antibiotic, which can lead to antibiotic failure or resistance. Therefore, those who believe they are allergic should provide as much detail to their physicians as possible about the reaction.

Allergic reactions occur when the immune system begins to recognize a drug as something foreign. True allergic reactions include rashes, such as hives (raised, intensely itchy spots that come and go over hours) and flat, blotchy rashes that spread over days but do not change by the hour; angioedema (swelling of the tissue under the skin, commonly around the face); throat tightness; wheezing; coughing; trouble breathing from asthma-like reactions; and anaphylaxis, a life-threatening allergic reaction that presents with symptoms of low blood pressure, difficulty breathing, abdominal pain, swelling of the throat or tongue and/or diarrhea or vomiting.[7]

Antibiotics only work to treat bacterial infections.

Myth: A prescribing regimen is unnecessary to follow as long as the antibiotics are taken.

Fact: Taking antibiotics incorrectly can affect their absorption, which can reduce or eliminate their effectiveness. It's important to know how many pills to take and how often to take them. In addition, some antibiotics need to be taken with something in the stomach, such as a glass of milk or some crackers, while others need to be taken only with water. Antibiotics also must be stored properly. Many children's antibiotics need to be refrigerated, while others are best left at room temperature.[1]

Myth: Once a person begins to feel better, the course of antibiotics can be discontinued.

Fact: Following through and taking the entire course of antibiotics is important for healing. If treatment is stopped

midcourse, the bacteria may be only partially treated and not completely killed, allowing them to become resistant to the antibiotic and cause reinfection.[1]

Myth: Antibiotics rarely interfere with other medications.

Fact: Antibiotics can have interactions with other prescription and nonprescription medications. Some examples include the antibiotic Biaxin, which should not be taken with Reglan, a digestive system drug; the antibiotics Flagyl and Protostat (metronidazole), which can cause problems when taken with the blood thinner Coumadin; and macrolide antibiotics, such as clarithromycin, erythromycin and azithromycin, which can boost blood levels of the antihistamine Hismanal (astemizole) to dangerous — and potentially lethal — levels.[1,8]

Taking antibiotics incorrectly can affect their absorption, which can reduce or eliminate their effectiveness.

Antibiotics also can often alter the way other drugs are metabolized. For instance, it is well-documented that the antibiotic erythromycin can make birth control pills less effective.[9] Therefore, it is important for patients to tell their doctors and pharmacists which other medications they are taking before being prescribed an antibiotic.

Myth: Alcohol should never be consumed when taking antibiotics.

Fact: Many people believe that drinking alcohol while on antibiotic therapy can negate the effects of antibiotics. But, there are only three known interactions between alcohol and antibiotics: Isoniazid, which is used for treating tuberculosis, can interact with alcohol and cause toxic liver effects, so while on isoniazid, it is suggested to strictly stay away from alcohol. Erythromycin antibiotic can enhance alcohol absorption from the gut, thereby causing reddening of the skin. Metronidazole, which is prescribed for the treatment of female reproductive organ and oral infection, also is known to interact with alcohol and induce vomiting and nausea. Other than these scenarios, it is generally considered safe to consume alcohol within moderation while on antibiotics. Too much alcohol intake, however, directly interrupts the liver metabolism and can mar the breakdown and excretion of medications, including antibiotics.[10]

Myth: Antibiotics can't harm people.

Fact: People can be harmed by misusing antibiotics. Each day, 190 million doses of antibiotics are administered, 133 million of which are prescribed to nonhospitalized patients. Of these latter prescriptions, 50 percent are unnecessary because they are prescribed for colds, coughs and other viral infections. This can result in antibiotic resistance, which is a worldwide health problem that continues to grow.[11]

Antibiotic resistance occurs when strains of bacteria in the human body become resistant to antibiotics due to use and abuse of antibiotics.[11] As a result of these antimicrobial-resistant organisms, many infectious diseases are increasingly difficult to treat, including HIV infection, staphylococcal infection, tuberculosis, influenza, gonorrhea, candida infection and malaria. Between 5 percent and 10 percent of all hospital patients develop an infection from antimicrobial-resistant organisms, 90,000 of whom die each year as a result of their infection, which is up from 13,300 patient deaths in 1992.[12]

Dispelling the Myths Now

Many patients ask or expect doctors to prescribe antibiotics when they feel sick. And, more often than not, doctors give in to patients' requests, even when patients are not sick with a bacterial infection — the only type of infection antibiotics can treat. In addition, patients often don't follow the prescribed treatment for antibiotics. Both physicians and patients must do their part to decrease the misuse of antibiotics, and that can begin by dispelling the myths about these miracle drugs. ❖

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

References

1. Antibiotics. eMedicineHealth. Accessed at www.emedicinehealth.com/antibiotics/article_em.htm.
2. The History of Antibiotics. Experiment-Resources.com. Accessed at www.experiment-resources.com/history-of-antibiotics.html.
3. The Truth About Antibiotics. About.com: Infectious Diseases. Accessed at infectious diseases.about.com/od/treatment/a/antibiotic_myth.htm.
4. Bacterial Infection or Virus? DukeHealth.org. Accessed at www.dukehealth.org/health_library/advice_from_doctors/your_childs_health/bacterial_infections.
5. Guidelines for Prophylaxis Antibiotics of Endocarditis (SBE). The Heart Surgery Forum. Accessed at www.hsforum.com/stories/storyReader$1448.
6. American Heart Association. New Guidelines Regarding Antibiotics to Prevent Infective Endocarditis. Accessed at www.americanheart.org/presenter.jhtml?identifier=3047051.
7. Solensky, R. Patient Information: Allergy to Penicillin and Related Antibiotics. UpToDate, September 2010. Accessed at www.uptodate.com/contents/patient-information-allergy-to-penicillin-and-related-antibiotics.
8. Graedon, J. Dangerous Drug Interactions. GeneralHealthTopics.com. Accessed at general healthtopics.com/dangerous-drug-interactions-365.html.
9. Dr. Kevin's Column: Frivolous Use of Antibiotics Can Be Dangerous. RxMagazine.com, November 10, 2000. Accessed at http://rx.magazine.tripod.com/kc_20001110.htm.
10. Interactions of Alcohol with Antibiotics. Samrx Blog. Accessed at www.samrx.com/blog/antibiotics/interactions-of-alcohol-with-antibiotics.
11. American College of Physicians. Antibiotic Resistance. Accessed at www.acponline.org/patients_families/diseases_conditions/antibiotic_resistance.
12. Antibiotic Resistance (Drug Resistance, Antimicrobial Resistance). MedicineNet.com. Accessed at www.medicinenet.com/antibiotic_resistance/article.htm.

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Plasma Exchange: New Uses for a Therapeutic Workhorse

TPE, or plasmapheresis, is effective for an expanding range of serious clinical disorders.

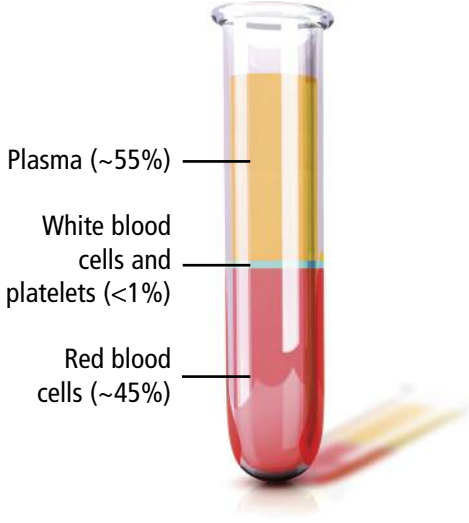
by KEITH BERMAN, MPH, MBA

THE IDEA OF removing harmful substances in the blood by apheresis — from the Greek *aphairesis* meaning "taking away" — originated nearly a century ago in Baltimore. In 1914, Dr. John Abel and his team at Johns Hopkins Medical School repeatedly removed quantities of blood from dogs, discarded the liquid plasma portion and reinfused the cellular blood elements with an isotonic salt solution. The dogs tolerated the procedure well.[1]

Dr. Abel coined the term "plasmapheresis" for this experimental procedure, and suggested that "if this method can be employed without harmful consequences, it is probable that it could be applied in a bolder manner in a greater variety of morbid states" than the old and now-discredited practice of simple bloodletting. Decades later in 1951, Dr. José A. Grifols Lucas — a member of the family that founded Grifols, a leading multinational plasma fractionator — published landmark research demonstrating the feasibility of plasmapheresis as a potential means to routinely collect donor plasma for purification into products such as albumin, clotting factors and immunoglobulins.

It would not be until the 1960s, however, that major engineering advances made it safe and practical to separate, remove and replace the plasma portion of blood in humans. These advances suddenly made it possible to collect plasma from donors on a regular basis, just in time to meet the growing needs of manufacturers that fractionate human plasma into critical therapeutic proteins.

But for the medical community, which had long struggled to help patients with serious blood hyperviscosity syndromes and drug-resistant autoimmune disorders, plasmapheresis offered a powerful new treatment tool. Today plasmapheresis — more accurately *therapeutic plasma exchange (TPE)* — is an established treatment modality for an impressive range of renal, hematologic and neurological disorders (Table 1).



TPE Basics

In the U.S., plasma separation from whole blood is most commonly accomplished by centrifugation, and involves the use of sophisticated, software-controlled equipment, disposable kits and other supplies. Alternatively, membrane separation technology may be used in conjunction with dialysis equipment (Figure 1). Plasma containing the toxic antibodies or other macromolecules is removed, discarded and replaced with 5% human albumin or, for certain rare hematological disorders, with donor fresh frozen plasma.

The therapeutic principle behind TPE is simple: to acutely reduce circulating blood levels of the toxic substance — most commonly harmful IgG or IgM antibodies — to allow for recovery and healing. To achieve this, five to six TPE procedures, each removing around one to one-and-a-half "plasma volumes," are usually required.

Multiple repetitions of the procedure are needed because less than half of the IgG antibody in the body actually circulates in the blood. The rest can be found in the extravascular compartment, including the lymphatic system. So while a single TPE procedure removes roughly 60 percent to 75 percent of the intravascular IgG, the circulating IgG level partly recovers due to re-equilibration of *extravascular* IgG that enters the bloodstream. Generally, the goal of a series of TPE procedures is to reduce the circulating IgG level by at least 70 percent to 85 percent.[2]

Plasma exchange has now been in clinical use for nearly five decades. One would think that by now every disease for which TPE might potentially provide a benefit has been evaluated and proved or disproved. But that is not at all the case. Thanks to an evolving understanding of mechanisms and variations in certain immune-mediated diseases and carefully focused clinical research, several important therapeutic applications for TPE have recently been identified and incorporated into standard clinical practice.

TPE for Exacerbations in Demyelinating CNS Disease

Either in instances where a patient inadequately responds to intravenous immunoglobulin (IVIG) therapy or as first-line therapy, TPE is established as effective for treatment of two relatively rare demyelinating autoimmune neuropathies: chronic inflammatory demyelinating polyneuropathy (CIDP) and a closely related disorder, Guillain-Barré syndrome.[3] But in multiple sclerosis (MS), a far more common demyelinating disease of the central nervous system affecting about 400,000 Americans, the question of whether TPE offered therapeutic benefit remained unanswered for many years.

Plasma exchange has now been in clinical use for nearly five decades.

The problem was due in part to the fact that MS has differing clinical presentations, which likely reflect different underlying disease variants. More than four in five patients start out with a relapsing-remitting course with exacerbation of symptoms, followed by partial resolution. Others start and remain on a chronic progressive course. To complicate things further, many patients with relapsing-remitting disease advance to a secondary progressive phase. In a number of studies, TPE has failed to show evidence of benefit against progressive forms of MS.[1]

Then, in 1999, a randomized, double-blind trial showed that TPE therapy achieved a dramatically higher response rate (42.11 percent vs. 5.9 percent) than sham TPE treatments in patients with a mix of MS and other central nervous system (CNS) demyelinating disorders suffering acute, severe attacks that failed to respond to high-dose steroids. More than a decade later — in its first revised guidelines for the use of TPE in 15 years — the American Academy of Neurology (AAN) concluded that TPE as adjunctive therapy is "probably effective" and "should be considered for adjunctive

Table 1.
Disease states for which therapeutic plasma exchange is an established therapy

Renal
Goodpasture's syndrome (anti-glomerular basement membrane disease)
Wegener's granulomatosis (associated rapidly progressive glomerulonephritis)
Renal transplantation; antibody-mediated rejection
Neurological
Guillain-Barré syndrome
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Lambert-Eaton myasthenic syndrome
Multiple sclerosis (relapses in steroid-resistant patients)
Myasthenia gravis; myasthenic crisis and pre-thymectomy
Paraproteinemic polyneuropathies
Hematologic
Cryoglobulinemia
Drug-associated thrombotic microangiopathy
Hyperviscosity in monoclonal gammopathies
Thrombotic thrombocytopenic purpura (TTP)
Others
ABO-incompatible hematopoietic stem cell transplantation
PANDAS (exacerbation)
Sydenham's chorea
Wilson's disease; fulminant hepatic failure with hemolysis

Source: Szczepiorkowski, ZM, Winters, JL, Bandarenko, N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice — Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis. *Journal of Clinical Apheresis*, 2010;25:83-177.

treatment of exacerbations in relapsing forms of [steroid-resistant] MS."

The new AAN guidelines also encourage neurologists to consider TPE for treatment of other fulminant CNS demyelinating diseases that fail to respond to high-dose corticosteroid treatment. These include neuromyelitis optica (NMO), associated with vision loss and eye pain, and transverse myelitis, which can cause weakness, numbness and paralysis of the arms and legs.

TPE for ABO-Incompatible Kidney Transplantation

Kidney transplantation is the ideal treatment for end-stage renal disease. Unfortunately, a severe shortage of donor kidneys has created a waiting list that has grown to well over 80,000 patients. Between 4,000 and 5,000 patients on that waiting list will die this year before a human leukocyte antigen (HLA)-matched kidney becomes available.

Living donor kidneys have helped to fill the gap; more than four in 10 transplanted kidneys now come from a living donor. But even here, another barrier has often stood in the way of finding a suitable donor: ABO incompatibility.

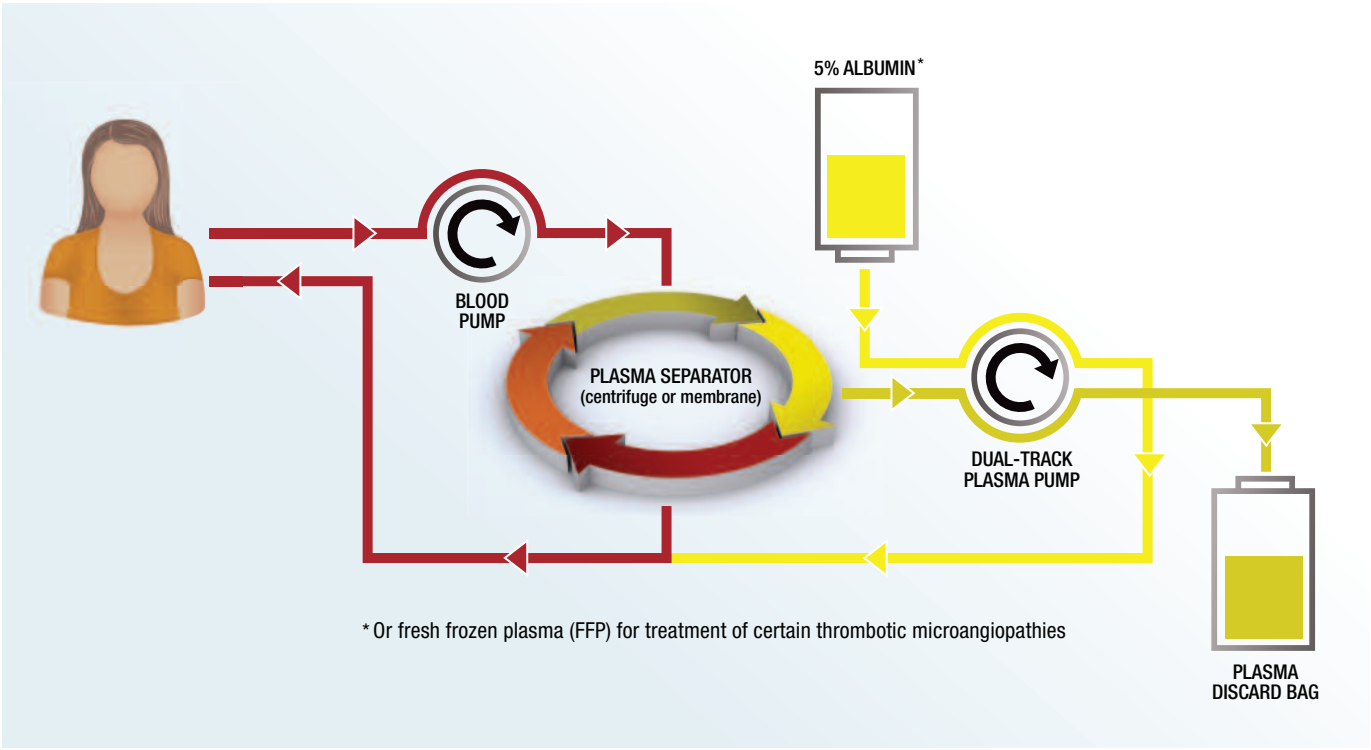
Consider a transplant candidate with an O blood type. She has neither A nor B antigens on her own red blood cells, kidneys or other body tissues. But she *does* have naturally occurring antibodies in her bloodstream against both the A and B antigens. If she is transplanted with a kidney from a donor with the B blood type, her circulating anti-B antibodies will instantly target the "B" antigens all over those donor kidney cells, triggering within minutes or hours an acute or "hyperacute" rejection of that kidney.

There is at least a 35 percent chance that any two individuals are ABO-incompatible (ABO-I).[4] For years, surgeons could not transplant an otherwise well-matched kidney from an ABO-I living donor — typically a relative — leaving patients on the waiting list to deteriorate further or die before a suitable organ could be found.

Enter plasma exchange and the ABO-I "desensitization protocol." Typically used in conjunction with immunosuppressive drugs and IVIG, a short series of TPE procedures before and after transplantation physically removes most of the harmful anti-A or anti-B antibody that would otherwise cause rejection of the kidney graft.

Recently, specialists at The Johns Hopkins Hospital in Baltimore reported 100 percent one-year graft kidney survival in 53 consecutive ABO-I kidney transplants using their TPE and drug conditioning protocol.[5] "The current literature and our results indicate a critical role for TPE in ABO-I renal transplantation," they concluded.

Figure 1. Basic Therapeutic Plasma Exchange Process



What's Next for TPE?

Much like other immunomodulatory treatments whose effects are incompletely understood — think IVIG and tumor necrosis factor (TNF) inhibitors, for example — ongoing investigations promise to generate new future clinical applications for TPE. But if you'd like to pick just one to follow, consider work now being sponsored by Grifols. Six decades after Dr. Grifols Lucas' pioneering work in plasmapheresis, the company's Spanish and U.S. investigators are conducting clinical trials to determine whether TPE with 5% human albumin replacement can slow or reverse the progression of Alzheimer's disease.

Encouraged by laboratory and clinical findings in a small pilot study, Grifols is now completing a Phase II study randomizing 42 Alzheimer's patients with mild to moderate disease to receive either a series of 18 TPE treatments or an equal number of sham procedures.[7] The primary endpoint of this study is clearance of beta-amyloid peptide from the cerebrospinal fluid (CSF). Intensive TPE therapy removes circulating albumin-bound beta amyloid, creating a gradient that draws the toxic peptide from the CSF into the bloodstream, where some of it binds to endogenous and freshly infused albumin and in turn is removed in the next TPE procedure. A larger trial, set to start this year, will try to answer whether TPE in combination with IVIG at different doses and frequencies can slow cognitive decline or actually improve cognitive function.

Modern medicine remains helpless against this devastating neurodegenerative condition, which now affects some five million Americans. The Grifols Alzheimer's initiative is nothing if not a bold application of Dr. Abel's century-old plasmapheresis concept. If he were here today, he would certainly be pleased. ❖

References

1. Jones, JV. Plasmapheresis in Systemic Lupus Erythematosus. *Clinics in Rheumatology Disease*, 1982;8(1):243-60.
2. Brecher, ME. Plasma Exchange: Why We Do What We Do. *Journal of Clinical Apheresis*, 2002;17:207-11.
3. Cortese, I, Chaudhry, V, So, YT, et al. Evidence-Based Guideline Update: Plasmapheresis in Neurological Disorders. *Neurology*, 2011;74:294-300.
4. Montgomery, RA. ABO Incompatible Transplantation: To B or Not to B. *American Journal of Transplantation*, 2004;4:1011-2.
5. Tobian, AA, Shirey, RS, Montgomery, RA, et al. The Critical Role of Plasmapheresis in ABO-Incompatible Renal Transplantation. *Transfusion*, 2008 Nov;48(11): 2453-60.
6. Boada, M, Ortiz, P, Anaya, F, et al. Amyloid-Target Therapeutics in Alzheimer's Disease: Use of Human Albumin in Plasma Exchange as a Novel Approach for Aβ mobilization. *Drug News Perspectives*, 2009 Jul/Aug;22(6): 325-38.
7. Accessed at ClinicalTrials.gov: April 26, 2011.

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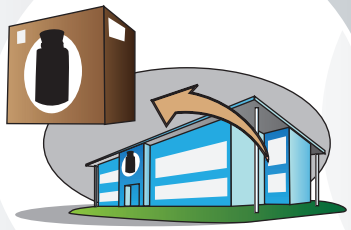

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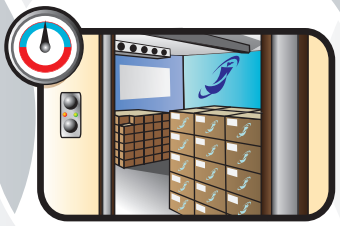

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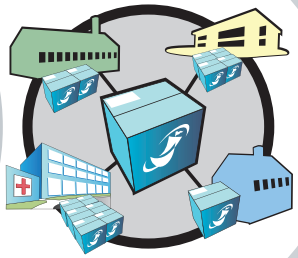

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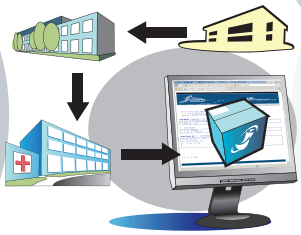

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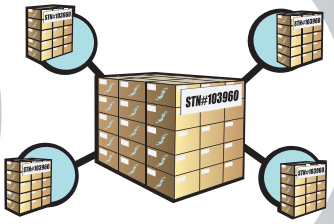

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"A great leader's courage to fulfill his vision comes from passion, not position." — John Maxwell

by TRUDIE MITSCHANG

FOR NEARLY A quarter of a century, Damian A. Braga has been a respected and influential leader within the vaccine industry. As he looks back over his career with sanofi pasteur, Braga is mindful of the fact that his rise to the top was a less-than-traditional one. After college, Braga devoted several years to a volunteer organization focused on eradicating poverty, and later joined his father in the music business. During that time, Braga decided to go to graduate school and earn his MBA in finance, a move that opened the door for him to accept a financial analyst position with a small company called Connaught Laboratories. That company would later become the global vaccine industry leader, sanofi pasteur.

Leadership that Capitalizes on Individual Strengths

"I held a number of different positions within the organization, which eventually led me to work closely with then-president and chief operating officer Dave Williams," recalls Braga. "Dave became a mentor and personal friend." It was Williams who helped influence so many of Braga's future business decisions, as well as his leadership style.

Braga joined the company in 1988, and his goal-oriented mindset, natural leadership abilities and approachable management style enabled him to move quickly through a range of senior-level positions, ultimately reaching the top of the Americas organization in late 2007.

Today, Braga serves as the president of sanofi pasteur U.S., and vice president, sanofi pasteur Americas, with 16 direct reports, many who have been with him for close to 10 years. He attributes part of the low turnover at sanofi pasteur to the company culture, which he believes ignites a passion for public health and innovation — values many employees personally share. As a leader, Braga stresses a personalized management approach that capitalizes on individual strengths. "Initially, I like to work closely with people so that I can get to know them, see how they make decisions, and how they handle challenges. Once I trust their judgment, I'm hands off. It's important to manage people individually to get their best contributions."

By combining a commitment to organizational growth with a strong sense of civic responsibility, Braga brings a unique leadership style to one of the world's leading vaccine manufacturers. Responsible for commercial operations in the U.S., Canada and Latin America business units, Braga oversees more than $3 billion (USD) in annual revenue and has served a vital role in the organization's global strategic planning and growth.

Braga notes that the vaccine industry has historically been volatile and unpredictable, influenced by everything from the rising tide of consumer concern over vaccine safety, to the unpredictability of biologic production. "There always seems to be ample opportunity for crises management," he says. "I learned very early that to succeed in this business, you have to demonstrate your ability to manage difficult situations and lead by example."

When Braga started his career with Cannaught Laboratories, the industry itself was somewhat small and commoditized, with little investment in innovation and development. At the time, the vaccine industry was also under assault and facing numerous lawsuits. "I am proud of the leadership role that sanofi pasteur has taken in creating a vibrant vaccine industry," Braga says. "We've become a driver of innovation and safety and made numerous contributions to new and existing vaccines, further protecting lives."

Focusing on Future Accomplishments

Among sanofi pasteur's many accomplishments during Braga's tenure are the successful launch of a new adolescent and adult booster vaccine to protect against pertussis, tetanus and diphtheria;

a new meningococcal vaccine for children and adolescents; a pediatric formulation of influenza vaccine; and a high dose influenza vaccine for those aged 65 and older. "Until recently, the influenza vaccine for adults had pretty much remained unchanged in 40 years," he says. "Now, there is ample opportunity for improvement as we move to the next generation of vaccines targeting specific population groups."

The FDA approved sanofi pasteur's Fluzone High Dose for seniors last year, and the formula has made a significant contribution to the influenza vaccine marketplace, especially since people aged 65 and older are at high risk for influenza-related complications and fatalities. Sanofi pasteur has been working on other innovations in the influenza vaccine marketplace as well: On May 10, the FDA approved the company's supplemental biologics license application for licensure of Fluzone Intradermal (influenza virus vaccine). This intradermal delivery system for influenza vaccine uses a novel microinjection system, featuring an ultrafine needle that is 90 percent shorter than the typical needle used for intramuscular injection of influenza vaccine.

As a leader, Braga stresses a personalized management approach that capitalizes on individual strengths.

Looking ahead, Braga says the focus is now on adult vaccination schedules, with the goal being to promote the importance of vaccines to a generation that has forgotten what a significant

contribution immunization has made to public health. Last year, Braga made the bold decision to embark on a public service partnership with the American Academy of Pediatrics (AAP) in an effort to raise vaccine awareness and directly confront the anti-vaccine messaging that had become so prevalent. "It brought us to the forefront of the debate, and I'm proud that we stepped up to the plate and took a position," he says. "I especially wanted to work with a group like AAP that has credibility with physicians. If we can give physicians the tools and information they need when they speak with parents, we can make a difference."

In recent years, the vaccine industry has not only been challenged by ongoing debates about vaccine safety, but also by unforeseen threats like the H1N1 pandemic. While the events surrounding the pandemic seem like a distant memory to some, Braga says for those who were on the frontlines during the outbreak, it's time to give credit where credit is due: "I am extremely proud of efforts that were made, especially within our organization. Our people worked around the clock to deliver a vaccine in a very short period of time. The handling of the H1N1 pandemic was a tremendous success, and I think it is important to remind everyone of the things that went right."

Other research and development projects within the organization include addressing strain-specific influenza concerns; promoting adult pertussis vaccination; and maintaining a leadership position in emerging markets like Latin America, where the company already has a strong presence. Currently, sanofi pasteur is developing a vaccine for Dengue fever, a mosquito-borne illness that infects as many as 100 million people each year, most in Latin America. Recently, Dengue has erupted in parts of Florida and Texas. Dengue is characterized by fever, headache and rash, and in some instances can lead to life-threatening complications such as severe internal bleeding and even death.

A Vision for Making a Difference

"Our vision is for a world in which no one suffers or dies from a vaccine-preventable disease, and it's a lofty one," says Braga. "We are dedicated to using all of the resources at our disposal to continue making significant contributions to public health and, ultimately, making a difference in people's lives." ❖

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

Overcoming Resistance

Once considered a "super drug," antibiotics are becoming increasingly ineffective against a host of new "super bugs." Retiree Betty Gordon provides a glimpse into what it's like to live with a growing list of relentless infections.

by TRUDIE MITSCHANG

MANY MEDICATIONS HAVE unwanted side effects, although most subside once a patient completes the prescribed dosage. Unfortunately, this is not always the case when it comes to antibiotics. Once considered a "super drug," antibiotics have been prescribed successfully for decades to treat all manner of bacterial infections. But for patients with chronic conditions requiring multiple, ongoing courses of antibiotics, a dangerous and lingering side effect can be resistance to those antibiotics, along with a host of opportunistic infections.

Antibiotic resistance occurs when antibiotics no longer work against disease-causing bacteria. These infections are difficult to treat and can mean longer-lasting illnesses, more doctor visits or extended hospital stays, and the need for more expensive and toxic medications. Some resistant infections can even cause death. Or in Rhode Island resident Betty Gordon's case, symptoms can manifest as a series of life-hampering infections that simply never go away.

Antibiotic-resistant patient Betty Gordon enjoys family time with her grandchildren, Austin and Olivia, her daughter, Michelle, and son-in-law, Bill.

The Disease that Caused the Resistance

Betty suffers from primary immunodeficiency disease (PIDD), although this chronic illness went undiagnosed for decades. Sick off and on since age 4, Betty endured numerous bouts of sinusitis and pneumonia and had been on antibiotics for most of her adult life. She finally was diagnosed with PIDD at the age of 57. "After a failed sinus surgery, I was correctly diagnosed with PIDD by my ENT, but I still had to argue with other doctors who simply did not believe I had an immune disease," recalls Betty. "They said I didn't seem sick enough, although I certainly felt sick enough."

In the small community where Betty lives, she found it difficult to get the specialized healthcare she needed. Her quest eventually led her to see an immunologist in Boston who, since 2004, has taken her through a series of antibiotics trying to find the right fit. Her current regimen, which she started in 2011, seems to be working so far, says Betty. To manage her PIDD symptoms, Betty performs weekly subcutaneous infusions of immune globulin. For a while, says Betty, she felt pretty good, but gradually the years she'd spent on antibiotics treating the symptoms rather than the root of her illness began to take their toll.

Feeling very much like a guinea pig, Betty says she has tried more antibiotics than she can name.

On an Antibiotic Roller Coaster

"For the past three years, it seems I'll be on an antibiotic that I've taken effectively forever and suddenly I can't take anymore," explains Betty.

"Macrobid was the first antibiotic that began giving me problems. While taking it I felt extremely tired and anxious. Next, my doctor prescribed Augmentin, and I reacted with horrible diarrhea, so we switched to Biaxin … and the list goes on."

Like many people her age, Betty's first introduction to antibiotics was penicillin, a drug she handled well until she developed a small rash during a course of treatment and was (incorrectly) diagnosed with a penicillin allergy. Feeling very much like a guinea pig, Betty says she has tried more antibiotics than she can name, and the recurring sinus and yeast infections are a constant reminder of the toll this regimen has taken on her body's equilibrium.

According to the Centers for Disease Control and Prevention (CDC), antibiotic resistance is defined as the ability of bacteria or other microbes to resist the effects of an antibiotic. Antibiotic resistance occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals or other agents designed to cure or prevent infections. The bacteria survive and continue to multiply, causing more harm.

For Betty, who has seen dozens of doctors in her quest to feel better, a major frustration has not only been the trial-and-error approach to treatment, but what she views as a lack of collaboration within the healthcare system as a whole. "If I could make one suggestion to doctors, it's that I wish that they would take the time to pick up the phone and check with other specialists on their patient's healthcare team," says Betty. "I know that can be time-consuming for a patient like me; I have a primary care doctor, an immunologist, an allergist and a hematologist. But if even a few of them had gotten together to develop a treatment plan, I might not be as sick as I am today."

Preventing Antibiotic Resistant Infections

According to the Centers for Disease Control and Prevention (CDC), healthcare providers and patients can play a role in preventing the spread of antibiotic resistance.

Advice for Healthcare Professionals

- Prescribe antibiotic therapy only when it is likely to be beneficial to the patient.
- Use an agent targeting the likely pathogens.
- Use the antibiotic for the appropriate dose and duration.
- Visit www.cdc.gov/getsmart/antibiotic-use/antibiotic-resistance-faqs.html to view the CDC's adult and pediatric Academic Detailing Sheets for providers.

Advice for Patients

- Talk with your healthcare provider about antibiotic resistance: Ask whether an antibiotic is likely to be beneficial for your illness, and find out what else you can do to feel better sooner.
- Do not take an antibiotic for a viral infection like a cold or the flu.
- Do not save some of your antibiotic for the next time you get sick. Discard any leftover medication once you have completed your prescribed course of treatment.
- Take an antibiotic exactly as the healthcare provider tells you. Do not skip doses.
- Complete the prescribed course of treatment even if you are feeling better. If treatment stops too soon, some bacteria may survive and reinfect.
- Do not take antibiotics prescribed for someone else. The antibiotic may not be appropriate for your illness. Taking the wrong medicine may delay correct treatment and allow bacteria to multiply.
- If your healthcare provider determines that you do not have a bacterial infection, ask about ways to help relieve your symptoms. Do not pressure your provider to prescribe an antibiotic.

Taking Matters into Her Own Hands

For some antibiotic-resistant patients, lifestyle changes can help. Betty keeps a humidifier in her room, for example, to help treat the recurring sinus headaches. She also takes acidophilus supplements to ease the digestive distress she battles constantly. As far as diet, Betty avoids milk products and sticks to a very simple daily menu of protein, fruits and vegetables to try to ward off potential infections.

"As a PIDD patient, you want to avoid a hospital stay at all costs," she explains. "No matter what I do, I have to plan my life carefully, because you just never know when you are going to be sick again. I live with some type of infection every day — it just never gets better." ❖

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

BioProducts

New Generation Elisa/IFA Analyser

The Mago4 is a new generation of Elisa/IFA (immuno-fluorescence assays) analyzer for use in hospital immunology and microbiology departments. Its easy-to-use "open" multifunction analyzer operates as an Elisa instrument, as well as offers IFAs, serum agglutination and hemagglutination. It offers positive identification of samples, disposable tips capability and a Windows XP software platform. Once processing is underway, the graphical interface provides the operator with continuous information on batch progress. A color display shows which tubes have been processed and indicates whether errors, such as insufficient samples, have been encountered. Results can be exported into Excel. The system also can accommodate assays from other companies.

Labmedics, 0161 869 0420 (United Kingdom), www.labmedics.co.uk/Diamedix-Mago4.asp

Patient Portal

Informatics' new patient portal includes a monthly calendar with a simplified, user-friendly layout of patient visits; lab results, including medications, medical conditions and visit summaries; a messaging component that allows direct communication between patient and physician; and educational content offering disease-specific information based upon a patient's diagnosis. The portal is accessible from all browsers, enabling patients to view their medical data anytime from anywhere with Internet connectivity. Patients have the ability to make simple annotations, although they are unable to delete or change information in their files. The portal also includes three data availability categories: immediate, delayed and restricted. Certain results are delayed for a number of days, giving the physician time to review and discuss the results with the patient prior to entering the information into the patient portal. Other results are restricted, based upon facility policies or legal requirements to maintain confidentiality of certain healthcare data.

Informatics Corp. of America, (615) 866-1500, www.icainformatics.com

High Alert Medication Label

A new high alert line-tracing label is the newest of Medi-Dose's customizable line-tracing labels available for laser or thermal printers. The labels are for medications not already covered by preprinted labels, including heparin, epidurals, chemotherapy, insulin, oxytocin, magnesium sulfate, paralytics, narcotics and IV nutrition. The pharmacy places the entire label on an IV infusion container. When the medication is administered at the bedside, nursing applies one line label to each end of the tubing, which facilitates line traces.

Medi-Dose/EPS, (800) 523-8966, www.medidose.com

Lifestyle Medicine Program

FirstLine Therapy is a lifestyle program that provides physicians with the education and tools they need to treat patients with lifestyle medicine in order to avoid or reduce risk factors for chronic illnesses. The program reflects recommendations from the National Institutes of Health and the latest scientific studies, and includes clinically tested protocols for enhanced nutrition, exercise and stress-management recommendations, as well as a certification for physicians and key staff and guidance for insurance reimbursement. An onsite three-day implementation service is included to help integrate the program quickly.

Metagenics Inc., (800) 692-9400, www.firstlinetherapy.com

IV Lock Box

The Lock-To-Pole IV lock box, made of clear PETG (an amorphous thermoplastic) for everyday durability, protects controlled substance infusions from tampering and locks to the IV pole to prevent the unit from being stolen. It is available with a standard key or keyless digital lock. The box accommodates IV bag sizes up to 1,000 mL and locks to pole sizes up to 7/8 inches in diameter. The kit includes one foot of plastic chain and a plastic connecting link to connect the chain to the hook on top of the box.

Health Care Logistics, (800) 848-1633, www.healthcarelogistics.com

BioResearch

Summaries of up-to-date clinical research published internationally.

Higher SCIG Dosing Results in Lower Infection Rate and Fewer Missed School/Work Days

Treatment with a higher dose of subcutaneous immunoglobulin (SCIG) correlates with reduced risk of infection and fewer missed school or work days in patients with primary humoral immunodeficiency (PI), according to findings from separate U.S. and European trials of CSL Behring's Hizentra 20% SCIG product.

In an overall study population comprising 84 PI patients, 46 received a weekly dose of 120.0 mg/kg body weight, while 38 others received a weekly dose of 208.2 mg/kg body weight (all mean of medians) over either 28 or 54 weeks. While both studies documented clear evidence of effectiveness of SCIG with zero acute serious bacterial infections, patients on the higher of the two doses had a lower annualized infection rate (2.76 vs. 5.18 infections/patient/year) and fewer missed days from school or work (2.06 vs. 8.0 days/patient/year).

The blood IgG nadir following a dose increased by 23.8 percent in patients assigned to the higher SCIG dose, compared with just 8.6 percent in those on the lower dose of SCIG. Local reactions to infusion and treatment-related adverse events were more commonly reported with the higher dose of SCIG, but those reactions were primarily mild to moderate in severity. "These data suggest that the higher dose of Hizentra provides greater protection from infection and its consequences in patients with primary immunodeficiencies," the study's lead author concluded.

Hagan, J. Subcutaneous immunoglobulin replacement therapy for primary immunodeficiency: High-dose versus low-dose treatment using Hizentra. 2011 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (San Francisco, Calif.), Mar. 21, 2011. Oral abstract #4602.

Type of Factor VIII Replacement Product Does Not Affect Inhibitor Risk in Previously Untreated Hemophilia A Patients

Noting that a number of studies have explored the impact of the type of factor VIII replacement therapy on inhibitor development in hemophilia A patients with conflicting results, Italian investigators performed a systematic review and meta-analysis of published trials to evaluate new inhibitor rates in previously untreated patients (PUPs) with severe hemophilia A.

Data from a total of 800 patients enrolled in 25 quality-selected prospective studies published between 1990 and 2007 were included in this review. Overall, the inhibitor incidence rate did not differ significantly between recipients of plasma-derived and recombinant factor VIII concentrates (weighted means: 21%, 95% CI, 14%-30% vs. 27%, 95% CI, 21%-33%). Similarly, rates of high-titer inhibitors did not differ significantly between patients treated with plasma-derived (weighted means: 14%, 95% CI, 8%-25%) or recombinant factor VIII concentrates (weighted means: 16%, 95% CI, 13%-20%). The investigators concluded that the type of factor VIII product "does not seem to influence the inhibitor rate in PUPs with severe hemophilia A."

Franchini, M, Tagliaferri, A, Mengoli, C, et al. Cumulative inhibitor incidence in previously untreated patients with severe hemophilia A treated with plasma-derived versus recombinant factor VIII concentrates. Critical Reviews in Oncology/Hematology, *2011 Jan 27 [Epub ahead of print].*

Prophylaxis Prevents Bleeds and Arthropathy in Children with Hemophilia A (the ESPRIT Study)

A multinational European research team has reported findings from a randomized controlled trial that compared the efficacy of prophylaxis with episodic (on-demand) therapy in children with severe hemophilia over a 10-year time period. The objective of this study was to learn whether a prophylaxis strategy reduces the incidence of joint bleeds (hemarthroses) and image-proven joint damage.

Forty-five children with severe hemophilia A, aged 1 to 7 years with negative clinical-radiologic joint score at entry, were consecutively randomized to prophylaxis with recombinant factor VIII (25 IU/kg three times weekly) or on-demand therapy with ≥25 IU/kg every 12 to 24 hours until complete resolution of clinical bleeding. Ultimately, 21 children were assigned to prophylaxis and 19 to on-demand treatment. Children on prophylaxis had fewer joint bleeds than children on on-demand therapy: 0.20 vs. 0.52 events per patient per month ($P<0.02$). Plain-film radiology showed signs of arthropathy in 29 percent of patients on prophylaxis vs. 74 percent receiving on-demand treatment ($P<0.05$).

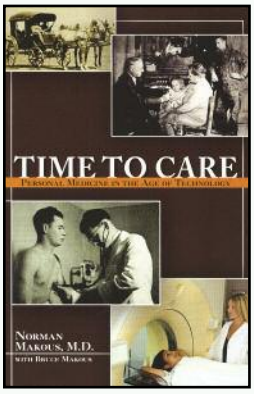
Prophylaxis was more effective when started before 36 months of age; that subset of patients experienced fewer joint bleeds (0.12 joint bleeds per month) and no radiologic signs of arthropathy. This randomized trial confirms the efficacy of prophylaxis in preventing bleeds and arthropathy in children with hemophilia, particularly when it is initiated early in life.

Gringeri, A, Lundin, B, von Mackensen, S, et al. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). Journal of Thrombosis and Haemostasis, *2011 Apr; 9(4):700-10.*

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

BioResources

Recently released resources for the biopharmaceuticals marketplace.



Time to Care: Personal Medicine in the Age of Technology

Author: Norman Makous, MD

In *Time to Care*, Dr. Norman Makous, who has spent 60 years providing personal care to his cardiology patients, examines how the high cost of technology-based care has caused the economic squeeze in healthcare that has already led to the rationing of medical services. He proposes that the patient-doctor relationship can be brought back to the center of the healthcare system to humanize treatment, improve quality and reduce unnecessary spending. The book is filled with dozens of real-life case anecdotes that illustrate the crucial role of the patient-doctor relationship and how medical practice has changed in recent decades.

www.brucemakous.com

Gene Expression Profiles in Peripheral Blood for the Diagnosis of Autoimmune Diseases

Author: Dr. Bertalan Mesko

This article, published in the biomedical review journal *Trends in Molecular Medicine*, examines whether peripheral blood can be used for the diagnosis of autoimmune diseases or the prediction of the effectiveness of therapies. It includes a decision tree, as well as a set of proposed guides to facilitate interdisciplinary collaborations. The article will be emailed free upon request.

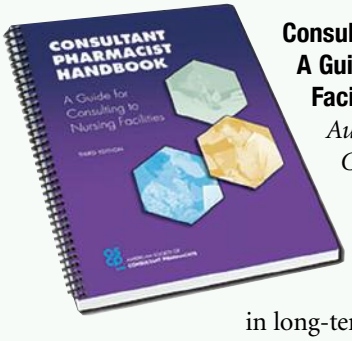
scienceroll.com/2011/03/21/gene-expression-profiles-in-peripheral-blood-for-the-diagnosis-of-autoimmune-diseases

Leveraging IV Room Automation for Improved Safety and Cost Control

Author: Baxa Corp.

This white paper describes how intravenous (IV) room automation can impact patient safety. It includes a review of the effect of technology on operational efficiency in the IV room, lists the core benchmarks for evaluating IV room technologies, and outlines which tools pharmacists can employ to assess IV room automation. The paper can be downloaded for free.

pppmag.com/digitalmag/Main.php?MagID=5&MagNo=36



Consultant Pharmacist Handbook: A Guide for Consulting to Nursing Facilities (3rd edition)

Author: American Society of Consultant Pharmacists

The new third edition of this comprehensive, how-to guide for consultant pharmacists addresses new issues in long-term care that include MDS 3.0 and the Quality Indicator Survey (QIS). Also included is additional information on disposal of unused medications; additional guidance about controlled substance ordering, storage and accountability; and an update on the proposed new Quality Measures recently released for public comment.

www.med-pass.com/shopping/shopexd.asp?id=89&MarketID=1800000&CategoryID=1810300

Pharma Readiness for Personalized Medicine

Author: Diaceutics

Diaceutics' new report analyzes which drug companies are best prepared to capitalize on new discoveries in genetic biomarkers and translate them into personalized medicine. It also looks at how traditional drug development has changed since the advent of personalized medicine, as well as the ways that leading pharmaceutical companies have adapted. Included are interviews with top officials from the leading drug companies about the changes they anticipate from new discoveries in personalized medicine, including genomic science, biomarker advances and information technology, as well as the challenges and opportunities they see ahead. The full report is available for $3,500.

www.diaceutics.com

Competitor Analysis: Coagulation Factors 2011

Author: Research and Markets

This report provides a competitor evaluation in the field of plasma-derived and recombinant coagulation factors for topical and systemic administration to treat hereditary or acquired coagulation disorders as of January 2011. Included is a compilation of current active projects in research and development and a list of company-specific research and development pipelines. The downloadable pdf report includes six months of online access to the report data and any updates since the publication date.

www.researchandmarkets.com/research/963c7c/competitor_analysis

BioDashboard

CALCULATOR

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective July 1, 2011 through September 30, 2011.

Product	Manufacturer	HCPCS	Hospital Outpatient ASP+5% (per gram)	Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$61.589	$62.176
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$69.928	$70.594
GAMMAGARD LIQUID	Baxter BioScience	J1569	$75.378	$76.096
GAMMAGARD S/D	Baxter BioScience	J1566	$61.589	$62.176
GAMMAPLEX	Bio Products Laboratory	J1599	$75.838*	$75.838
GAMUNEX-C	Grifols	J1561	$74.639	$75.350
PRIVIGEN	CSL Behring	J1459	$69.445	$70.106

*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, 30 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	PIDD
GAMUNEX-C (Liquid, 10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Grifols	PIDD, ITP, CIDP
GAMUNEX-C (Liquid, 10%, SCIG)	1 g, 2.5 g, 5 g, 10 g, 20 g	Grifols	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

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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