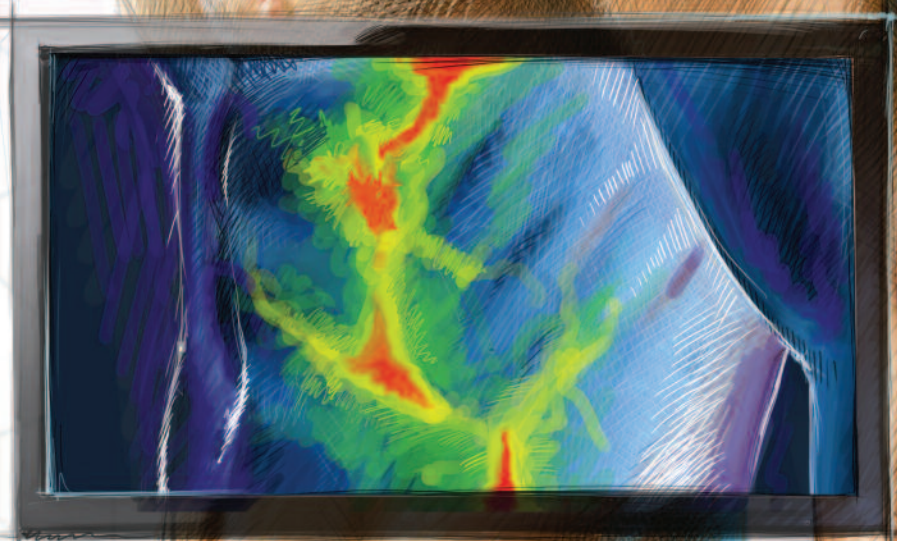
October 2011

BioSupply Trends

Special Focus: INNOVATION

Quarterly

Molecular Imaging



Imagine
A World Without Vaccines

What's New
in Diabetes and Cardiovascular Drugs

Nuclear Accidents:
Fukushima vs. Chernobyl

Myths & Facts:
Fibromyalgia

Under the Skin Is In — Page 52

Now available in 500 and 1000 IU vials

wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

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.

To report suspected adverse reactions, contact:

Octapharma USA, Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch

Please see Highlights of Prescribing Information.

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 now available in two new vial sizes and convenient single box packaging

- **500 IU VWF:RCo and 500 IU FVIII activities in 5 ml**
- **1000 IU VWF:RCo and 1000 IU FVIII activities in 10 ml**
- **Includes Mix2Vial transfer device**

NDC Number	Size
67467-182-01	500 IU VWF:RCo and 500 IU FVIII activities in 5 mL
67467-182-02	1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL

For More Information, Please Contact Us

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121 River Street
Suite 1201
Hoboken, NJ 07030
201-604-1130
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uscustomerservice@octapharma.com
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888-429-4535

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

www.wilateusa.com

octapharma
For the safe and optimal use of human proteins

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

INDICATIONS AND USAGE

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

DOSAGE FORMS AND STRENGTHS

- Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:
  - 500 IU VWF:RCo and 500 IU FVIII activities in 5 mL
  - 1000 IU VWF:RCo and 1000 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.**

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.
- Reconstitute 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.

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.

NDC Number	Size	Protein Amount
67467-182-01	500 IU VWF:RCo and 500 IU FVIII activities in 5 mL	≤ 7.5 mg
67467-182-02	1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL	≤ 15.0 mg

HOW SUPPLIED/STORAGE AND HANDLING

- 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.
- 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

Distributed by:

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octapharma

For the safe and optimal use of human proteins

BioSupply Trends Quarterly

October 2011

Features

Special Focus: Innovation

About BioSupply Trends Quarterly
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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.

Back to the Future

IT'S BEEN SAID that those who cannot remember the past are condemned to repeat it. While innovation is usually linked with progress — and great innovations associated with transformational advancements — sometimes a link to the past is necessary to prevent regression. As dark allows us to understand light and famine gives us a new appreciation of feast, so does history offer the backdrop to value the innovative developments that current generations unintentionally take for granted.

Imagine a world without vaccines. As I write this, vaccine proponents are trying to minimize the damage from an uninformed comment made from an influential political platform. Misinformation, unfortunately, produces unintended consequences, and those on the front lines of the healthcare industry know all too well how difficult education regarding vaccine safety and efficacy has been since an anti-vaccine movement grew from myths, half-truths and false innuendos. We have covered this subject numerous times, as recently as our last publication in my letter to you. But at some level, repetition — staying the course — may be exactly what is needed to turn the tide of the anti-vaccine movement, and reach those who feel paralyzed by the uncertainty it has created.

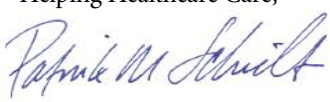
Our feature, A World Without Vaccines, illustrates not "a world," but "our world" just a century ago. It was a world that bore little resemblance to today. In the early 1900s, the infant mortality rate was a shocking 20 percent because common childhood killers such as measles, diphtheria, smallpox and paralytic polio went unchecked, leaving thousands of victims in braces, crutches, wheelchairs and iron lungs. Today, these devastating diseases have been contained because of the development and distribution of safe, effective and affordable vaccines. Yet, though vaccines have been called the most transformative public health achievement of our time, current U.S. measles outbreaks are at a 15-year high, and more than 18 million people worldwide continue to be infected by this highly contagious disease each year. Our catalog feature, Miracle Medicines, brings to light that although preventive vaccines are as common as household cleaning products, apathy and lack of education could potentially reverse years of disease reduction and eradication, thereby turning our backs to the future.

As we look forward in this innovation-themed issue to the future of molecular imaging, we also maintain an important perspective, understanding that these techniques that may hold clues to treatment or cures for currently intractable diseases are already decades old. Researchers have now combined what was once considered an enigmatic outpost of the nuclear age with new advances in gene therapy and personalized medicine. Long known for its advances in cardiology, molecular imaging now also has implications for such diseases as diabetes, tuberculosis and Alzheimer's.

A fresh look at the link between diabetes, and heart disease and stroke, provides insight into the new anti-diabetic and cardiovascular drugs now available, highlighting the need to balance innovations in treatments with the lifestyle changes that prevent the onset of these deadly diseases.

We honor the past as we look to an exciting future where once-prominent diseases will continue to be minimized or even eradicated as history has shown can happen. As always, we hope you find this issue of *BioSupply Trends Quarterly* informational, educational and helpful to you in your practice. ❖

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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EEOC Issues Final Regulations Interpreting the ADA Amendments Act

Effective May 24, final regulations published by the Equal Employment Opportunity Commission (EEOC) protect many more employees from disability discrimination in the workplace than had previously been the case under the courts' narrow interpretations of the Americans with Disabilities Act (ADA) and the ADA Amendments Act (ADAAA).

According to an EEOC press release, "The ADAAA and the final regulations keep the ADA's definition of the term 'disability' as a physical or mental impairment that substantially limits one or more major life activities; a record (or past history) of such an impairment; or being regarded as having a disability. But the law made significant changes in how those terms are interpreted, and the regulations implement those changes."

The regulations provide a list of principles to guide the determination of whether a person has a disability, including that an "impairment need not prevent or severely or significantly restrict performance of a major life activity to be considered a disability." Whether an impairment is a disability should be construed broadly, to the maximum extent allowable under the law. And, with one exception (ordinary eyeglasses or contact lenses), "mitigating measures," such as medication and assistive devices like hearing aids, cannot be considered when determining whether someone has a disability. Impairments that are episodic (such as epilepsy) or in remission (such as cancer) are disabilities if they would be substantially limiting when active.

The regulations also clarify that the term "major life activities" includes "major bodily functions," such as functions of the immune system, normal cell growth, and brain, neurological and endocrine functions. And, not every impairment will constitute a disability. Examples of impairments that should easily be concluded to be disabilities, such as HIV infection, diabetes, epilepsy and bipolar disorder, are provided.

Last, the regulations make it easier for individuals to establish coverage under the "regarded as" part of the definition of "disability." Establishing such coverage used to pose significant hurdles, but under the new law, the focus is on how the person was treated rather than on what an employer believes about the nature of the person's impairment.

Two question-and-answer documents about the regulations are available to the public and employers to help them understand the law and new regulations at www.eeoc.gov/laws/statutes/adaaa_info.cfm. For a complete list of the final regulations, go to www.federalregister.gov/articles/2011/03/25/2011-6056/regulations-to-implement-the-equal-employment-provisions-of-the-americans-with-disabilities-act-as. ❖

Part D Drug Premiums to Decrease in 2012

The average monthly premium for Medicare Part D prescription drug coverage will decline in 2012, according to the U.S. Department of Health and Human Services (HHS). The average monthly drug plan in 2012 will cost about $30, approximately $1 lower than 2011 averages. In addition, nearly 900,000 Medicare beneficiaries whose prescription drug purchases place them in the so-called "doughnut hole" have benefited from the new 50 percent discount on covered name-brand drugs.

"The marketplace created by the Medicare Part D structure continues to be vibrant and highly competitive," said Mary R. Grealy, president of the Healthcare Leadership Council. "To succeed, Part D plans have to keep premiums affordable and provide value, and seniors are benefiting." ❖

Healthcare Reform Rule Bans Unreasonable Premium Increases

In May, the Department of Health and Human Services (HHS) issued a final regulation to ensure that large health insurance premium increases will be thoroughly reviewed and consumers will have access to clear information about those increases. Effective Sept. 1, the rule requires independent experts to scrutinize any proposed increase of 10 percent or more for most individual and small group health insurance plans. States will have the primary responsibility for reviewing rate increases, and HHS will serve in a backup role in states that don't have the resources or authority to review rates. HHS has awarded $44 million in Affordable Care Act grants to states to help strengthen their oversight capabilities. An additional $200 million will continue to be available to states under the Act.

The final regulation also requires that as of September 2012, the 10 percent threshold will be replaced by state-specific

thresholds that reflect the insurance and healthcare cost trends in each state. HHS will work with states to develop those thresholds. The rule also requires insurance companies to provide consumers with easy-to-understand information about the reasons for unreasonable rate increases and post the justification for those hikes on their websites, as well as on the HHS Affordable Care Act website (www.healthcare.gov).

Publication of the final rule comes as health insurance companies have reported some of their highest profits in years. One cause for these profits is that actual medical costs are growing more slowly than what insurance companies projected when they set their 2011 rates last year. However, many of the rates consumers and small employers pay today don't reflect these lower costs.

"Effective rate review works; it does so by protecting consumers from unreasonable rate increases and bringing needed transparency to the marketplace," said HHS Secretary Kathleen Sebelius. "During the past year, we have worked closely with states to strengthen their ability to review, revise or reject unreasonable rate hikes. This final rule helps build on that partnership to protect consumers." ❖

Legislation Protects the Treatment of Rare Diseases

Two new bipartisan bills, H.R. 2672 and S. 1423, both titled Preserving Access to Orphan Drugs Act, have been introduced to safeguard the development of drugs and therapies that treat patients with rare diseases by eliminating barriers to innovation. Under the current law, most plasma protein therapies, despite being approved for marketing by the U.S. Food and Drug Administration solely for the treatment of one or more rare diseases or conditions, would not qualify for the orphan drug exclusion from the annual pharmaceutical fee. In the U.S., a rare disease or condition is generally defined as one affecting fewer than 200,000 people. The new bills would modify the law to ensure that manufacturers can exclude the sale of all drugs and therapies that are FDA-indicated solely for the treatment of one or more rare diseases from their annual fee liability.

"The majority of patients who rely on plasma protein therapies are coping with a very rare disease for which no alternative treatment exists," said Julie Birkofer, Plasma Protein Therapies Association senior vice president, North America. "This legislation preserves access to therapies and drugs for rare disease patients and helps to ensure that research and development into new therapies for orphan diseases continues to be encouraged and remains unencumbered." ❖

Reimbursement FAQs

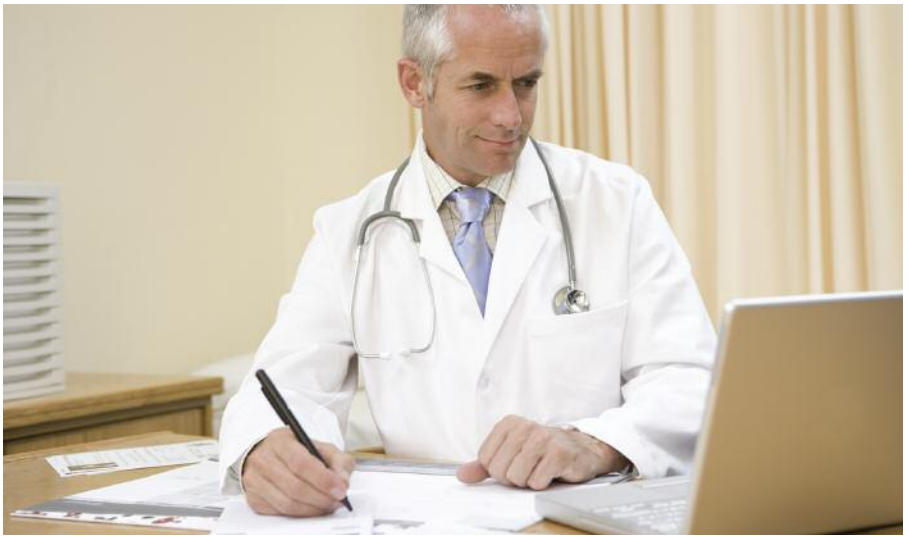
Some commonly held misunderstandings about reimbursement are clarified.

Does Medicare reimburse for intravenous immune globulin (IVIG) when used to treat autoimmune hemolytic anemia (AIHA)?

Although it is not routine, Medicare does reimburse for IVIG in patients with refractory AIHA in some instances. Specifically, local coverage determination for at least one of the durable medical equipment (DME) Medicare administrative contractor (MAC) providers states:

"In this condition, intravenous immune globulin is indicated only for those patients who have failed to respond to other forms of therapy and/or require rapid cessation of hemolysis due to severe or life-threatening manifestations of this condition. Duration of treatment is generally a short course of 3-5 weeks. Realizing dosage may vary based on patient's individual situation, dosage must be in keeping with the recommended current literature and standard of practice." ❖

I have many patients who cannot afford the care they need. In addition, many do not qualify for entitlement programs because their income is not low enough. Are there any programs to help get my patients the care they need?



There are several programs that offer prescription and/or insurance premium assistance. To qualify for many of these programs, it is not necessary to be below the federal poverty level. In almost all cases, patients are required to give personal information such as proof of income and expenses to substantiate their need. In addition, healthcare providers need to be prepared to fill out forms validating the diagnosis.

Some of the programs that will assist patients:

Patient Services Inc. will offer premium and/or copay assistance help for patients with hereditary angioedema, bleeding disorders, chronic inflammatory demyelinating polyneuropathy, complement-mediated diseases, primary immunodeficiency and more. For a complete list of diseases or to refer patients, go to https://www.patientservicesinc.org.

Needy Meds provides a database of information on different assistance programs. It does not directly supply medications or provide financial assistance. Providers and patients using this free service can search the database by disease, drug name, program name or company name to find applicable assistance programs. To read more about Needy Meds, go to http://www.needymeds.org/index.htm.

The National Organization for Rare Disorders administers patient assistance programs for uninsured and underinsured patients with rare diseases such as chronic non-infectious uveitis, multiple sclerosis and primary immunodeficiency. Programs may include assistance for premiums, copayments, travel and lodging for certain clinical trials. The type of help a patient qualifies for depends on the disease and/or medication. To view a complete program list, go to http://www.rarediseases.org/patients-and-families/patient-assistance. ❖

Is there any help for low-income seniors who rely on Medicare Part D plans to assist with out-of-pocket expenses for medications?

It is a well-known fact that patients who can afford their medications are likely to be more compliant and, as a result, have fewer complications. Seniors on a fixed income can become especially vulnerable to noncompliance because of an inability to afford their medications. Additionally, because they are on an entitlement program, they do not qualify for manufacturer assistance programs. However, there may be some assistance that many Medicare recipients are not accessing.

The Centers for Medicare and Medicaid Services (CMS) recently reported that they believe nearly two million people qualify for but are not enrolled in a subsidy assistance program for low-income Medicare recipients. Beneficiaries with limited resources and with incomes less than $16,335 a year for an individual or $22,065 for a couple may qualify for the Medicare Low Income Subsidy program. CMS reports that it is easier for beneficiaries to qualify than in years past. A person's house, car and life insurance policies do not count as resources. For a full list of qualifications and to apply for assistance, patients can go to http://www.ssa.gov/prescriptionhelp. ❖

Now that Gammagard Liquid has been added to the External Infusion Pump LCD as covered subcutaneous immune globulin, what billing codes must be used for reimbursement?

For reimbursement of Gammagard Liquid for dates of service on or after July 22, 2011, the existing Healthcare Common Procedure Coding System (HCPCS) code must be used: J1569 — Injection, Immune Globulin (Gammagard Liquid), Intravenous, Nonlyophilized (e.g. Liquid), 500 mg. For subcutaneous administration, only an E0779 infusion pump is covered, and a JB modifier must be added to each HCPCS code: J1569-JB. No modifier should be added for other routes of administration.

Gammagard Liquid is available in 1 gram (2 units of service [UOS]) and 2.5 gram (5 UOS) sizes. Suppliers must choose the package size that is appropriate for the dosage being administered to minimize waste. For example, one unit of service (1 UOS) is 500 mg. If 1,500 mg is prescribed (3 UOS), two 1 gram vials (4 UOS) must be used rather than one 2.5-gram vial (5 UOS). Excess waste due to non-optimal vial sizes will be denied as not reasonable and not necessary.

Gammagard Liquid will be added in a future revision of the Local Coverage Determination (LCD). Suppliers should refer to the LCD, policy article and supplier manual for additional information. ❖

New Blog! Reimbursement Unraveled

Check out our new Reimbursement Unraveled blog 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 column is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

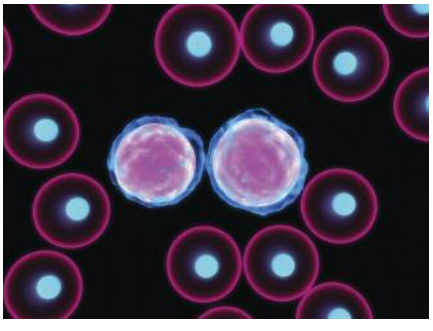
FDA Approval

Baxter Receives FDA Approval for Gammagard Liquid

Baxter International has received U.S. Food and Drug Administration approval for subcutaneous administration of Gammagard Liquid 10% (immune globulin infusion [human]) for patients with primary immunodeficiency. According to Richard Schiff, Baxter's gammaglobulin trials medical director, "Building upon years of strong clinical data of Gammagard Liquid, our subcutaneous clinical trial in patients with PI demonstrated efficacy consistent with that seen in other clinical studies of intravenous and subcutaneous immune globulin." Gammagard Liquid is indicated as replacement therapy for primary humoral immunodeficiency in adult and pediatric patients 2 years of age and older. ❖

Medicines

FDA Approves Rituxan for Two Rare Disorders



The U.S. Food and Drug Administration has approved Rituxan (rituximab) in combination with glucocorticoids (steroids) to treat patients with Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA), two rare disorders that cause blood vessel inflammation (vasculitis). Rituxan is an antibody that works by greatly reducing the number of specific immune cells in the blood, known as B cells.

In a single controlled trial, 197 patients with WG or MPA were assigned at random to receive either Rituxan plus glucocorticoids once a week for four weeks or oral cyclophosphamide plus glucocorticoids daily to induce remission. After six months, 64 percent of patients treated with Rituxan had complete remission compared with 53 percent of patients treated with cyclophosphamide. Retreatment with Rituxan was not formally evaluated. Therefore, more data are needed to determine the safety of more than one course of Rituxan, as well as its long-term safety. ❖

Medicines

FDA Approves Menactra for Infants from 9 Months

Menactra, a vaccine for the prevention of invasive meningococcal disease for children ages 9 months and older has been approved by the U.S. Food and Drug Administration. The vaccine had previously been approved for patients ages 2 through 55. The approval for the younger age comes after one Phase II and three Phase III modified single-blind, controlled, multicenter clinical trials involving more than 3,700 patients that included safety data for children as young as 9 months. Among babies ages 9 to 12 months, the most commonly reported adverse events included irritability and tenderness at the injection site. And, the likelihood of fever was similar to that found among other pediatric vaccines. ❖

Research

Vaccine Prevents Heroin High in Animals

Researchers are seeing promising results in animals from a vaccine designed to prevent a heroin high. The new heroin vaccine, which targets both heroin and a chemical produced by its breakdown, produces antibodies that appear to prevent heroin from reaching the brain and producing euphoria. In a study conducted at the Scripps Research Institute, addicted rats that were given the vaccine also were less likely to self-administer more heroin, in contrast with the ones that did not get the vaccine. The findings were released online in advance of print publication in the *Journal of Medicinal Chemistry*.

Since heroin abuse and addiction also help drive the spread of HIV through needle sharing, the researchers are now exploring whether it might be possible to combine an HIV vaccine and a heroin vaccine into the same injection. The same researchers also have produced vaccines that try to stop the effects of cocaine and nicotine, both of which are currently being tested in humans. ❖

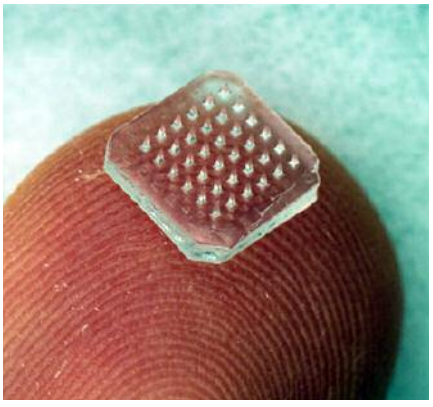
Did You Know?

"The healthcare law's discount on brand-name drugs for some Medicare beneficiaries has been used by 48,000 people who saved a combined $38 million — $800 on average — through the first two months of this year."

— Department of Health and Human Services

Research

Grant Makes Needle-Free Vaccine a Reality



Nanopatch, a needle-free vaccine delivery system, is a step closer to reality after a consortium of investors donated $15 million to aid the Australian Institute for Bioengineering and Nanotechnology in developing it. Nanopatch has thousands of small projections to deliver vaccines to abundant immune cells in the skin, doing away with needles inserted into muscle, where there are few immune cells. Early stage testing in animals has shown that a nanopatch-delivered flu vaccine is effective with only 1/150th of the dose compared with a syringe.

In addition to being more effective, the nanopatch is expected to reduce needle stick injuries and cross-contamination, and it does not need refrigeration like traditional vaccines, which could cut costs and make transportation easier. "In Africa, about half of vaccines aren't working properly because of a breakdown in the cold chain," says Mark Kendall, a professor at the institute. Money from Australia's federal government's innovation investment fund has helped establish the new company, Vaxxas, which will commercialize the vaccine. ❖

Research

HPV Vaccine Reduces Cervical Abnormalities

In a study in Australia, the HPV vaccine Gardasil helped to reduce the number of teenage girls who develop cervical abnormalities by as much as 50 percent. The vaccine appeared, however, to have much less impact on older women.

In the study, which took place in the state of Victoria, researchers compared Pap smear test results of girls after they received the Gardasil vaccine in a national, public-funded vaccination program in 2007 and 2008 with test results of earlier batches of girls who were never vaccinated. Results of the study showed that proportionately fewer girls (.42 percent) vaccinated with the Gardasil vaccine developed high-grade cervical abnormalities compared with unvaccinated girls (.8 percent).

"In conjunction with the data from our colleagues in the sexual health field, who have already demonstrated a significant reduction in the occurrence of genital warts since the vaccine program started, we are optimistic that this is an indication that the vaccine program is already beginning to have an impact," said Julia Brotherton, an epidemiologist with the Victorian Cytology Service Registries. The study appeared in *The Lancet* journal. ❖

Research

Study Tests an Adjuvant to Vaccinate Newborns

A new approach developed at Children's Hospital Boston that uses an adjuvant (an agent to stimulate the immune system) along with a vaccine shows that newborns may be able to be vaccinated and protected from disease. The multinational study, funded by the United Kingdom's Medical Research Council and the Bill & Melinda Gates Foundation, stimulated blood samples from 120 Gambian infants with a panel of different toll-like receptors (TLRs) and measured production of cytokines from white blood cells — all elements of the immune response that are difficult to elicit in newborns. The infants ranged from newborn to 12 months old, allowing the researchers to examine age-specific effects to see if the adjuvants remained effective over time.

Results showed that many of the TLR agonists elicited some form of immune response, but a thiazoloquinoline compound, stimulating TLR7 and TLR8, elicited the greatest productions of the cytokine TNF-alpha, a key component of the immune response during the first month of life, and it was the only compound to elicit production of the cytokine interferon gamma in newborns. "Currently, until an infant gets the full vaccination series, he or she is not fully protected," said Ofer Levy, MD, PhD, of Children's Division of Infectious Diseases. "The adjuvant could be combined with any vaccine, and if things work very well, it could provide single-shot protection at birth." ❖

Research

Test Can Predict Immune Responses to Flu Shots

Researchers at the Emory Vaccine Center at Emory University, Atlanta, Ga., have developed a method for predicting whether someone will produce high levels of antibodies against a flu shot a few days after vaccination. Based on a series of clinical studies during the annual flu seasons in 2007, 2008 and 2009, healthy young adults were vaccinated with a standard flu shot (trivalent inactive vaccine), while others were given live attenuated vaccine nasally. Researchers then surveyed the activity levels of all human genes in blood samples from the volunteers, which revealed that the activity of many genes involved in innate immunity, interferon and reactive oxygen species signaling was changing after flu vaccination. They also identified genes necessary for cells to adapt to the stress of producing high levels of antibodies. Knowing the extent to which carefully selected genes are turned on in white blood cells, the researchers can predict on day three, with up to 90 percent accuracy, who will make high levels of antibodies against a standard flu shot four weeks later.

"The main goal of our study was to demonstrate the feasibility of predicting how strongly a vaccine will stimulate the immune system," says Bali Pulendran, PhD, professor of pathology and laboratory medicine at Emory School of Medicine and Yerkes National Primate Research Center. "Along the way, we have developed an assay that focuses on a handful of genes, which could be the basis for a customized vaccine chip to make these predictions cost-effectively." The researchers now want to examine whether the signatures that predict immune response to flu can predict responses to other vaccines. The results were published online July 10 in *Nature Immunology*. ❖

People and Places in the News

FDA/EU APPROVALS

The U.S. Food and Drug Administration (FDA) has recommended approval of Human Genome Sciences' and GlaxoSmithKline's **Benlysta**, the first new drug to treat patients who suffer from lupus. The drug works by inhibiting the production of antibodies that attack and destroy healthy tissue.

Octapharma USA's **octaplex** (human prothrombin complex, freeze dried) has been approved as a fast track product for reversal of anticoagulation therapy in patients under vitamin K antagonist therapy with the need for urgent surgery or invasive procedures.

NxStage Medical Inc. has received FDA clearance to market its **Therapeutic Plasma Exchange (TPE)** cartridge for use with the NxStage System One in a clinical environment. TPE is an extracorporeal blood purification technique to remove part of a patient's plasma, while replacing it with another substance such as fresh frozen plasma or a solution containing albumin. TPE may be performed to treat immunological, hematological and neurological disorders.

The U.S. Food and Drug Administration has approved **Roche**'s new test for human papillomavirus (HPV), the first one-pass test to specifically identify the two HPV strains that cause 70 percent of cervical cancers. Current HPV tests can detect the presence or absence of more than a dozen HPV types linked to cancer. But, Roche's new cobas 4800 test does that, as well as identifies whether a woman has HPV-16 or HPV-18.

CSL Behring has been granted orphan drug designations by the European Commission for the development of its recombinant fusion protein linking coagulation factor VIIa with albumin (rVIIa-FP), a novel therapy to treat hemophilia A and B patients with inhibitors.

Kedrion has received U.S. Food and Drug Administration approval to sell its albumin (Kedbumin) in the U.S. Kedrion will produce albumin for the U.S. market at its production plant in Bolognana, Lucca, Italy.

APPOINTMENTS

Sanofi has appointed **Greg Irace**, curently president and CEO of Sanofi's U.S. operations, to the newly created role of senior vice president, global services, and **Anne C. Whitaker** as president, North America, Pharmaceuticals.

The Clinical and Laboratory Standards Institute (CLSI) has hired **Luann Ochs**, MS, as the new vice president of standards development. Ochs will oversee the CLSI standards development process, including the creation, delivery and oversight of medical testing consensus standards, guidelines and other related laboratory reference products.

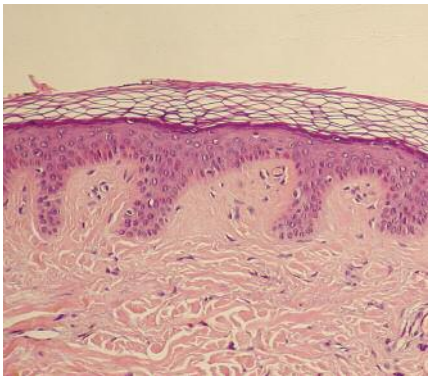
Portola Pharmaceuticals has named **Michael M. Kitt**, MD, as the company's senior vice president and chief medical officer. Dr. Kitt has clinically developed a number of novel compounds in multiple therapeutic areas.

Xencor Inc., a company using Fc engineering for the discovery and development of next-generation antibodies, has appointed **Edgardo Baracchini**, PhD, to chief business officer. Baracchini has

Vaccines

FDA Licenses New Intradermal Flu Vaccine

The U.S. Food and Drug Administration has approved Sanofi Pasteur's supplemental biologics license application for licensure of Fluzone Intradermal (Influenza Virus Vaccine). The vaccine is the first influenza vaccine licensed in the U.S. that uses a microinjection system for intradermal delivery. The vaccine's prefilled microinjection system features an ultra-fine needle that is 90 percent shorter than the typical needle used for intramuscular injection, and it is designed to consistently deposit vaccine antigens into the dermal layer of



the skin. The dermal layer contains a high concentration of specialized cells known as dendritic cells, which play a key role in generating an immune response. It contains 9 mcg of hemagglutinin per strain of influenza in a .1 mL dose (versus 15 mcg of hemagglutinin per strain of influenza in a .5 mL dose in the intramuscular Fluzone vaccine), yet in clinical trials the intradermal vaccine produced an immune response at rates similar to the intramuscular vaccine. Fluzone Intradermal is indicated for active immunization of adults 18 through 64 years old against influenza caused by the virus subtypes A and type B contained in the vaccine. ❖

more than 15 years of transactional experience, most recently as senior vice president of business development at Metabasis Therapeutics until its merger with Ligand Pharmaceuticals in 2009.

Dr. **Hilton Klein** has been named global vice president of science and new product introduction for the research models and services operating group at Harlan Laboratories.

NKT Therapeutics Inc., a privately held biotechnology company, has appointed **Barbara Finck**, MD, as chief medical officer. Finck was recently the senior VP research and development and chief medical officer at Osprey Pharmaceuticals.

Dr. **Miroslav Backonja** has joined Lifetree Clinical Research and Lifetree Center for Neuroscience Research as medical director. He was previously professor of neurology, anesthesiology and rehabilitation medicine at the University of Wisconsin Medical School in Madison, Wis., and a staff physician at the University of Wisconsin and Pain Treatment and Research Center.

ACQUISITIONS/ALLIANCES

Sanofi-Aventis has joined the **Massachusetts Life Sciences Center**'s Corporate Consortium Program, a quasi-public agency tasked with implementing the state's 10-year, $1 billion Life Sciences Initiative, which makes loans available to early-stage life sciences companies engaged in promising translational science and research.

GlaxoSmithKline and **Amplimmune** have entered a development agreement to focus on experimental drugs that target molecules that mask tumors and disease pathogens from the immune system. Early studies suggest the potential treatment can induce immune responses.

Sanofi-Aventis has established an alliance with the **Massachusetts Institute of Technology Center for Biomedical Innovation**, which will be known as the Sanofi-Aventis Biomedical Innovation Program (SABIP). SABIP will allow Sanofi-Aventis to develop therapeutic, diagnostic and prognostic applications based on the discoveries made during the alliance.

Roche Holding AG's **Genentech** unit is buying rights to **NovImmune SA**'s early stage compound, a so-called anti-IL-17 fully human monoclonal antibody, that may be developed to treat inflammatory and autoimmune diseases.

Intellikine, a La Jolla, Calif., biotechnology research company, has sold the global rights to develop treatments from molecules that target a family of immune system enzymes to **Infinity Pharmaceuticals**, Cambridge, Mass.

Emergent Biosolutions, a vaccines manufacturer, has purchased **Trubion Pharmaceuticals** to allow it to diversify its infectious diseases research pipeline.

Immunovaccine Inc. and **IRX Therapeutics** have entered into a preclinical research collaboration to evaluate the combination of IRX's primary cell-derived biologic, IRX-2, and DepoVax-based therapeutic cancer vaccines to generate a superior anti-tumor immune response and provide the foundation for the development of the next generation of therapeutic cancer vaccines. ❖

Research

Study to Assess Safety of Meningitis Vaccine During Pregnancy

A new study launched on World Meningitis Day (April 24) by the California Teratogen Information Service (CTIS) Pregnancy Health Information Line, a statewide nonprofit organization based at the University of California, San Diego, is enrolling women who have had exposure to a meningitis vaccine during the first trimester of pregnancy to determine the vaccine's safety. Participation involves two to four phone interviews and release of medical records relating to the woman's pregnancy.

"The meningococcal vaccine is not specifically recommended in pregnancy because it has not been well studied," explained Christina Chambers, PhD, MPH, UCSD professor of pediatrics and epidemiologics with a special focus in the area of birth defects prevention. "However, there is no data to suggest that this vaccine is harmful in pregnancy, which is why it's so important to closely study it so that pregnant women and their healthcare providers can make the best choices for treatment and prevention in mothers and babies." The study will be ongoing through 2015. ❖

FDA Approval

Kedrion Launches FDA-Approved Gammaked in U.S. Market

The U.S. Food and Drug Administration has approved Kedrion Biopharma's Gammaked, a 10 percent liquid, ready-to-use sterile solution of human immune globulin, for the U.S. market. Gammaked is approved for intravenous administration for primary immunodeficiency, idiopathic thrombocytopenic purpura and chronic inflammatory demyelinating polyneuropathy, and for subcutaneous administration to treat primary immunodeficiency. It is supplied in 1-, 2.5-, 5-, 10- and 20-gram single-use bottles. Kedrion has entered into an agreement with Grifols SA to manufacture Gammaked for the next seven years. And, as part of its ongoing expansion in the U.S., Kedrion began distribution of Gammaked on August 2 through designated channel partners. ❖

Research

Lower Cholesterol May Fight Infections

Researchers at the University of Edinburgh have found a direct link between the workings of the immune system and cholesterol levels. In a study in mice, the researchers discovered that a key immune hormone stimulated upon infection can lower cholesterol levels and thereby deprive viral infections of the sustenance they need to grow.

Currently, statins are prescribed to lower bad, or LDL, cholesterol, which helps to prevent heart attacks and strokes, and antiviral drugs and antibiotics are used to fight viral and bacterial infections, respectively. In the future, the researchers hope to use these findings to develop statin-like drugs that could both lower cholesterol and have potent anti-infective effects.

According to lead researcher Peter Ghazal, whose study was published in the *Public Library of Science (PLoS) Biology* journal, such treatments would help overcome the problems of drug resistance, since they would aim to enhance the way the body responds to an infection, instead of focusing on attacking the bug itself. ❖

Disease Guidelines

New Alzheimer's Diagnostic Criteria Are Finalized

The National Institute on Aging and the Alzheimer's Association have revised versions of an initial set of guidelines for diagnosing Alzheimer's disease. The final guidelines update the previous set developed 27 years ago and are intended for clinical purposes and for recruiting trial participants, rather than for diagnosing patients in routine practice. The new criteria incorporate results from brain imaging and spinal taps to determine if patients have dementia due to Alzheimer's disease; mild cognitive impairment due to Alzheimer's disease; and an entirely new entity called preclinical stages of Alzheimer's disease. The goal is to better ensure that patients really have Alzheimer's disease, as opposed to vascular dementia, Parkinson's disease dementia or other conditions with similar symptoms. ❖

One of these medicines is fake.
Can *you* tell which?

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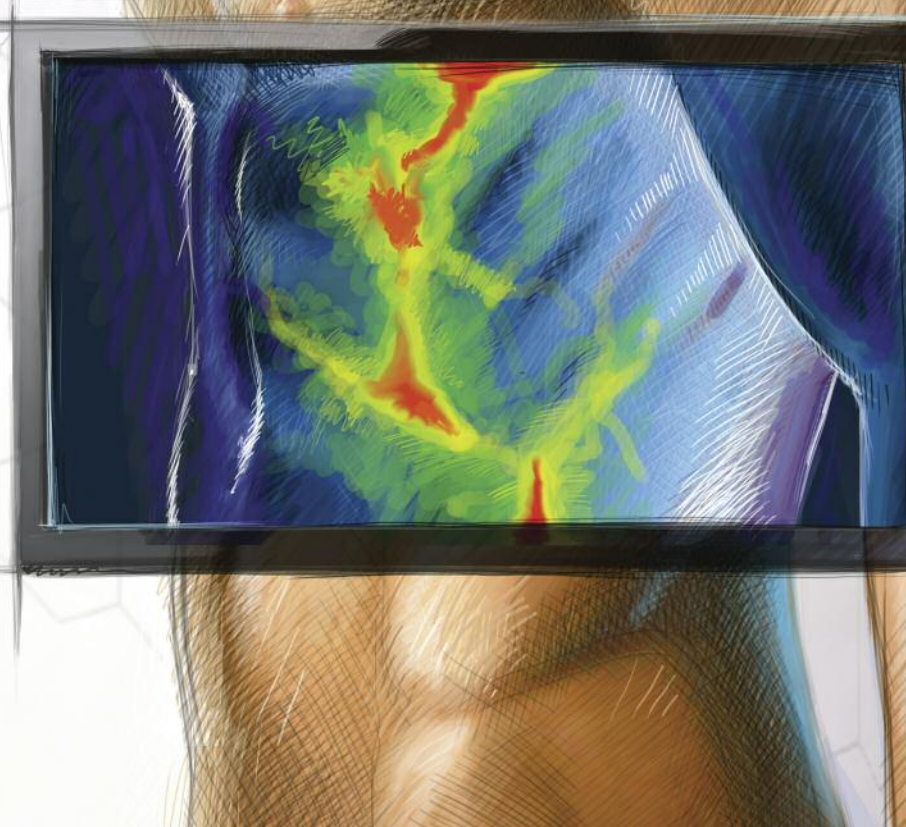
The Future of Molecular Imaging

Already decades old, techniques for molecular imaging may hold clues to treatment or cures for currently intractable diseases.

By John Otrompke

Outside of a few words muttered in a cardiology catheterization lab, few patients may have heard of the technique known as "molecular imaging." Yet the technique, which began in the context of nuclear medicine around the middle of the last century, may be so adaptable to modern advances in nanotechnology and gene therapy that it may be applicable to diseases as diverse as diabetes and Alzheimer's.

Although there are now multiple organizations encouraging research into molecular imaging, such as the new World Molecular Imaging Society (WMIS), the Society of Nuclear Medicine remains a mainstay conference for researchers in the field, and oncology remains the main area of medicine affected by molecular imaging.



A Brief History

The science and practice of molecular imaging began with the beginnings of the nuclear age. "Molecular imaging began to be called that in the late 1990s, but the practice of looking at molecular functioning in the whole body, in vivo, noninvasively, had been going on longer," says Dave Piwnica-Worms, MD, PhD, professor at Washington University School of Medicine in St. Louis, and director of the BRIGHT (Bridging Research with Imaging Genomics and High-Throughput) Institute at the university. "Right after World War II, the first form was the injection of I 131, a radioactive iodine, which was taken up by sodium iodide transporter in thyroid cancer patients."

According to Piwnica-Worms, modern methods of using the technique include radioactive isotopes, positron-emitting isotopes (PET), single photon emission computed tomography (SPECT) and newer methods such as fluorofores (used for optical imaging) and even bioluminescent agents such as firefly luminescence.

Notwithstanding the hoopla, most of the groundbreaking work going on in the molecular imaging field is in the basic science area, and application to humans is sometimes years away. It's still big news when an agent is approved by the U.S. Food and Drug Administration (FDA) or approved for reimbursement by government payers. For example, three years ago, a trade organization known as the Academy of Molecular Imaging was helpful in getting fluorodioxiglucose (FDG) scans, initially used in staging lung cancer, approved for reimbursement by Medicare — the first such approval ever, according to Robert Gillies, PhD, first president of the WMIS and vice chairman of radiation at the Moffitt Cancer Center in Tampa, Fla.

Perhaps counterintuitively, the biological nature and age of some of the first-generation agents currently approved for use and reimbursement in molecular imaging means that some of them are generic in nature. "There are in excess of two million U.S. studies per year done with FDG, which is a sugar where the radioisotope F18 is substituted," says Thomas Tulip, PhD, a business manager with experience operating medical imaging companies from the early days. "This tracer helps identify metastatic distal lesions, because the tumor is growing rapidly and requires more energy, and the modified glucose serves as fuel for the energy-demanding cancer cells."

Notwithstanding the widespread use of FDG, it is a generic tracer, says Tulip, who has been chief business officer for Dublin, Ohio-based Neoprobe for less than six months. "This material is an isotope that decays, with a 109-minute half-life, so it needs to be prepared relatively close to the location of ultimate patient use," explains Tulip, who notes that FDG is prepared by about 10 companies, and manufactured in 100 commercial centers.

While no one company owns the right to FDG, which was developed in the academic setting and made its way through the FDA through a consensus process involving a review of the literature, a number of new proprietary agents are now in the stages of research or being submitted to the FDA, such as a small molecule designed for the detection of plaques related to Alzheimer's disease, submitted to the FDA by Avid Pharmaceuticals, says Tulip.

"People are also developing tracers to look for active plaques in the heart system," says Piwnica-Worms, of Washington's BRIGHT Institute. "They are looking at receptors like myeloperoxidase in the blood vessels or on the heart cells to distinguish active plaques, which are more likely to burst, from stable plaques."

Now, says Piwnica-Worms, people have begun to combine the tools of gene cloning with tracers, noting that the BRIGHT Institute itself has been involved in the discovery of luciferase, an experimental imaging agent related to fireflies.

Notwithstanding the hoopla, most of the groundbreaking work going on in the molecular imaging field is in the basic science area, and application to humans is sometimes years away.

Consolidation May Spur Research

The increase in molecular imaging research in recent years has led to a number of changes in scientific and medical organizations in the field, including the consolidation of many organizations into the WMIS, which met for the first time in September in San Diego. "As of [September], the Academy of Molecular Imaging [merged] with the Society for Molecular Imaging [SMI] to form the WMIS," says Kim Pierce, executive director of the academy, which was formed in the 1980s as the Institute for Clinical PET. "The SMI was focused on basic science, while the academy focused on clinical applications," says Gillies. "The society was also heavily invested in optical imaging." Gillies notes that 40 percent of the society's members are involved in optical imaging.

Eventually, scientists expect the consolidation to affect the WMIS conference attendance and program. "Attendance is

Leading Abstracts from the First World Molecular Imaging Congress

While not all the authors of prize-winning abstracts at the September meeting of the World Molecular Imaging Society were able to waive the society's embargo, several were gracious enough to do so, and they proved illustrative both of the widespread potential for molecular imaging and its preponderantly basic science nature.

Winners include researchers from the Texas A&M Health Science Center and Stanford University, who have developed a "beta-lactamase reporter enzyme fluorescence (REF) system for real-time imaging mycobacterium infections in live mice," for use in measuring the existence and progression of tuberculosis, which otherwise is slowly progressing and difficult to diagnose. (Abstract T-198, "In-vivo Imaging of Mycobacterium Infected Mice Using Beta-lactamase Reporter Enzyme Fluorescence")

Researchers from the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital in Charlestown, also won a prize for their work preventing transplant failure in diabetic patients. The researchers used an siRNA-nanoparticle probe that targets beta-2 microglobulin, for both imaging and therapeutic purposes, to detect and prevent islet pancreatic transplants in mice. (Abstract T-095, "Preventing the rejection of pancreatic islet grafts using a siRNA-nanoparticle probe")

about 1,000 now, and in one year, we'd like to see it increase by 20 percent, and in five years, by 50 percent," says Dr. Paula Foster, PhD, a professor in the department of medical biophysics at the University of Western Ontario in London, who volunteers as chair of the program committee for SMI. This first year, the WMIS reflected many new areas of research, and it hosted a plenary session in conjunction with the Juvenile Diabetes Research Foundation. And, Dr. Foster says, in addition to areas of new research, she "could also see the program increase. Now, we have one day of education sessions and three days of scientific sessions, but I could see another day getting added on to the calendar. The new organization may also involve interest groups based around different modalities, or different disease categories. They may meet every evening during the meeting, and the WMIS may help them get set up organizationally and with fundraising, so eventually they may have their own meeting."

The increase in molecular imaging research in recent years has led to a number of changes in scientific and medical organizations in the field.

Innovative Molecular Imaging Research

Today, medical researchers enjoy two experienced scientific organizations at which to present their molecular imaging research. In addition to the World Molecular Imaging Conference, WMIS' annual meeting, the Society for Nuclear Medicine (SNM), which met this past June in San Antonio, hosted innovative presentations on the use of molecular imaging technology in disease states like Alzheimer's, immunological disease and breast cancer.

Neurology. "The plaque which is important in Alzheimer's disease is a little protein that clumps together and forms tiny lumps outside the neurons, called amyloid beta," says Christopher Rowe, MD, PhD, professor and director of nuclear medicine at the Center for PET at the University of Melbourne, Australia, who presented his research in the area at SNM and at the International Conference on Alzheimer's Disease in Paris this past summer.[1] "We can use PET studies to look at amyloid beta, a technique which was first developed at the University of Pittsburgh and in Sweden in 2002. If we're looking at the metabolism in the brain, we can use a radioactive form of glucose. The damaged areas of the brain have much less metabolism, so you will see a defect in those areas in a picture of the brain."

Although the presence of amyloid beta plaques correlates strongly with the risk of future Alzheimer's development, the course of the disease may be slow, suggesting the importance of early therapy should one of the experimental therapeutic agents for Alzheimer's disease ultimately be approved for general use, according to Rowe. For now, however, the use of molecular imaging in identifying amyloid beta plaques will be most useful as a diagnostic tool, he explains, adding that new techniques may be available clinically in the U.S. in the next year.

Data from clinical trials of an experimental agent known as Florbetapir were submitted to the FDA by Avid Radiopharmaceuticals and published in the *Journal of the American Medical Association*. Other agents also are being developed, such as florbetaben by Bayer and Flutemetamol by GE Healthcare, Rowe says.

Immunology. Other research, presented at SNM by Piwnica-Worms of the BRIGHT Institute, may lead to advances in stem cell transplants, a new frontline therapy for

some immunological conditions.[2] Piwnica-Worms and colleagues have published some research into molecular imaging in bone marrow transplant recipients. The technique has both diagnostic and therapeutic applications, and is beginning human trials, he explains.

"This research will look at bone marrow transplant patients who have leukemia or lymphoma," says Piwnica-Worms. "They get the transplant to kill off all the native bone marrow, then you give them the graft, in this case, an allogenic transplant from another donor. Now, we can use PET imaging to track where the cells go in the body," he says, adding that the trial was just approved to open up in humans. The technique has been tried in two human patients, and the researchers hope to get 10 enrolled in the Phase 1 observational trial.

"We hope we'll be able to follow whether the stem cells go to the spleen, liver or lung before going to the bone marrow," Piwnica-Worms explains, noting that one of the main risks of a bone marrow transplant is the danger of graft-versus-host disease (GVHD). "There's a danger that if the graft is a non-genetically matched donor cell, it can turn on the recipient. But the way this experimental retroviral construct is formed, it has a herpes simplex virus and kinase incorporated into it. If a patient got graft-versus-host disease, these donor lymphocytes have been engineered with a suicide gene delivered by the retrovirus, which when combined with a drug like gancyclovir would wipe out the donor lymphocytes that are producing the GVHD. Now, we've wiped out the bone marrow transplant, so they're back to the ICU, but at least they're still alive."

Oncology. Molecular imaging continues to spur new research in the oncology field. According to Tulip of Neoprobe, research in the field may result in not one, but two new agents for sentinel lymph node mapping coming onto the market in the next year. "Traditionally, in breast and lung cancers, one has surgery to excise some of the cancerous tissue, and one needs to understand how far the cancer has spread," says Tulip.

Previously, surgeons have used only an agent called blue dye in such procedures, because it was the only agent approved by the FDA for lymphatic mapping — until August, when the FDA approved another agent called sulphur colloid. But, both blue dye and sulphur colloid possess limitations, Tulip explains. "The [blue dye] injection frequently is painful, and there are some allergic reactions," he says. And, "some percentage of women actually get tattooed in the nodes with the blue dye. But the most important element with blue dye is the 10 percent to 20 percent false negative rate. Sulphur colloid also has a non-negligible false negative rate, and it has some issues as to how long it takes until it clears the injection site." But, with Neoprobe's experimental product, Lymphoseek, the sulphur colloid cleared the injection site within a matter of minutes, even though it was in the lymph nodes, whereas the process can easily take hours.

Neoprobe submitted a new drug application to the FDA last week for Lymphoseek, based on results from clinical trials presented at this year's meetings of the American Society of Clinical Oncology and SNM.[3,4]

Molecular imaging now has implications in the fields of numerous uncured diseases.

High Expectations for the Future

With researchers now combining molecular imaging with the latest advances in gene therapy and personalized medicine, what was once an enigmatic outpost of the nuclear age, generating diagnostic agents that were generic almost by nature, may have finally hit its stride.

While molecular imaging with its origins in the cardiology field was once predominantly used in oncology, it now has implications in the fields of numerous uncured diseases — from diabetes and bacterial conditions like tuberculosis, to the poorly understood diseases of the elderly such as Alzheimer's, to diseases that are themselves the consequences of some of our most modern medical treatments.

Whether the experimental uses of the techniques discussed above will ever make it into clinical use in humans is unknown for now, but with new mergers and associations coming to the field, it is clear that expectations are high. ❖

JOHN OTROMPKE, *JD, is a writer and professional speaker. He can be reached at John_Otrompke@yahoo.com or at 646-730-0179.*

Sources

1. Conversion from mild cognitive impairment to Alzheimer's disease over 12 months: Predictive value of A{beta} imaging with 18F-Florbetaben. Available online at http://jnumedmtg.snmjournals.org/cgi/content/meeting_abstract/52/1_MeetingAbstracts/170?eaf.
2. Abstracts of research performed at the BRIGHT Institute and presented at SNM. Available online at http://mic.wustl.edu/Publications/Publications.shtml.
3. 99mTc-tilmanocept (Lymphoseek) use in phase 3 sentinel node mapping study in squamous cell carcinoma (SCC) of the head & neck. Available online at http://jnumedmtg.snmjournals.org/cgi/content/meeting_abstract/52/1_MeetingAbstracts/100?maxtoshow=&hits=10&RESULTFORMAT=&fulltext=Neoprobe&andorexactfulltext=and&searchid=1&FIRSTINDEX=0& sortspec=relevance&resourcetype=HWCIT.
4. Prospective open label phase 3 trial of receptor-targeted 99mTc-tilmanocept for sentinel node evaluation in breast cancer and melanoma. Available online at http://jnumedmtg.snmjournals.org/cgi/content/meeting_abstract/52/1_MeetingAbstracts/599?maxtoshow=&hits=10&RESULTFORMAT=&fulltext=Neoprobe&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT.

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  - ≥ 13.3 log reduction of EMCV (HAV model)
  - ≥ 6.2 log reduction through 4% PEG precipitation and ≥ 5.5 log reduction through 20 nm nanofiltration of an experimental agent considered a model for the vCJD and CJD agents [3]

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

(1) Data on file, Instituto Grifols, S. A.
(2) Berger M. et al. Efficacy, Pharmacokinetics, Safety and Tolerability of Flebogamma® 10% DIF, a high purity human intravenous immunoglobulin in primary immunodeficiency. J Clin Immunol 2010; 30 (2): 321-9.
(3) Diez JM, 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), doi:10.1016/j.biologicals.2010.08.003.

For your convenience

- Liquid
- Room temperature storage 2-25° C (36-77° F) for the entire 2-year shelf life
- Three presentations: 5, 10 and 20 gram vials

Enhancing our commitment to you

- Every vial is laser etched with its own unique identifier number*, which helps to deter tampering and counterfeiting
- PediGri® On Line, unique to Grifols, offers full traceability from donation to the final product at **www.pedigri.grifols.com**

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

Important Safety Information

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

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

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

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

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

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

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

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

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

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

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

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

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

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

See the difference today

FDA04-1-US-10

GRIFOLS

Immune Globulin Intravenous (Human)
Flebogamma® 10% DIF
For intravenous use only
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BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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

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

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

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

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

WARNINGS AND PRECAUTIONS

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Post-marketing Experience

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

DO NOT FREEZE.

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

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

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What's New

By Jennifer Kester

Progress in the development of medications and treatments for America's deadliest diseases is fast-growing, but there is still much to be done.

Recent years have witnessed steady advances in the treatments for diabetes and cardiovascular disease, which remain among the foremost causes of death in the United States annually. Leading experts have long noted the strong link between the two diseases. According to the American Heart Association (AHA), heart disease and stroke are the No. 1 causes of death and disability among those with type 2 diabetes, and at least 65 percent of people with diabetes die from some form of heart disease or stroke. Plus, adults with diabetes are two to four times more likely to have heart disease or a stroke than those without diabetes. Because of the correlations between the two diseases, it makes sense to look at the current medicines being used to treat each of them when thinking about future treatments.

Diabetes and Cardiovascular Disease Today

Diabetes is the seventh leading cause of death among Americans, according to the Centers for Disease Control and Prevention (CDC). The American Diabetes Association (ADA) reports that 25.8 million children and adults have diabetes in the U.S., and seven million of them don't even know it. In 2010 alone, 1.9 million new cases were diagnosed among people age 20 and older. Diabetes is most prevalent in the African-American community, with 12.6 percent coping with the disease. The ethnic breakdown for other communities includes 11.8 percent of Hispanics, 8.4 percent of Asian-Americans and 7.1 percent of whites who suffer from the disease. Diabetes hits the elderly population the hardest, with 26.9 percent of those age 65 and older diagnosed. Overall, 11.3 percent of the 20-and-older age group have the illness.

in Anti-Diabetic and Cardiovascular Drugs

Cardiovascular disease is even more widespread in the U.S., with more than 81 million people having one or more forms of it, according to 2006 figures from the AHA. In fact, heart disease is the No. 1 cause of death in the U.S., the CDC says. And, the CDC reports that it's the leading cause of death for most ethnicities in the U.S.: In 2004, 25.8 percent of African-Americans, 19.8 percent of American Indians/Alaska natives, 24.6 percent of Asian-Americans, 22.7 percent of Hispanics and 27.5 percent of whites who died did so because of heart disease.

Heart Disease Medication

There are four types of cardiovascular disease, each with its own set of medications. The most common type, high blood pressure, is treated several different ways. To flush excess water and sodium from the body, diuretics are used. Beta-blockers reduce nerve impulses to the heart and blood vessels to make the heart beat slower and work less hard. Angiotensin-converting enzyme, or ACE, inhibitors prevent the formation of the hormone angiotensin II, which usually causes blood vessels to narrow. Angiotensin antagonists protect blood vessels from angiotensin II, which then leads to the vessels becoming wider. Calcium channel blockers, or CCBs, prevent calcium from entering the muscle cells of the heart and blood vessels, which causes the blood vessels to relax. However, CCBs have shown better results for African-Americans and older adults than ACE inhibitors or beta-blockers alone, according to recent studies. Alpha-blockers reduce nerve impulses to blood vessels, which allow blood to pass more easily. Alpha-beta-blockers are similar to alpha-blockers, but they also slow the heartbeat, like beta-blockers. This results in less blood being pumped through the vessels. Other medications that relax blood vessels are nervous system inhibitors, which control nerve impulses and cause the blood vessels to widen. Vasodilators open blood vessels by relaxing the muscle in the vessel walls.

The second most common form of cardiovascular disease is coronary heart disease. Aspirin is used to lower the risk of a heart attack for those who have already had one. In addition, aspirin has been shown to be effective in keeping arteries open in those who have had a previous heart bypass or similar artery-opening procedure. When pumping of the heart weakens, digitalis is prescribed to make the heart contract harder. Digitalis also slows some fast heart rhythms. Nitrates, including nitroglycerine, relax blood vessels and stop chest pain. Blood cholesterol-lowering agents like statins, niacin, fibrates and bile acid sequestrants are prescribed to lower LDL cholesterol levels in the blood. Thrombolytic agents are given during a heart attack to break up a blood clot in a coronary artery to restore blood flow.

Diabetes is the seventh leading cause of death among Americans, according to the Centers for Disease Control and Prevention (CDC).

Many of these medications also are used to treat coronary heart disease. In addition to alleviating blood pressure, ACE inhibitors help the damaged heart muscle pump blood better. Beta-blockers also assist with chest pain and ward off repeat heart attacks. Calcium channel blockers relax the muscles around the coronary arteries, which causes the blood vessels to open and increases blood flow to the heart. Diuretics also are used for treating coronary heart disease, since they decrease fluid in the body and help to reduce high blood pressure.

Strokes are the third most common type of cardiovascular disease. Aspirin is used as an antiplatelet/platelet aggregation inhibitor in stroke or transient ischemic attack, or TIA,

patients. It also can reduce the risk of a patient having another TIA or stroke. Clopidogrel (Plavix) is an antiplatelet/platelet aggregation inhibitor that helps prevent another stroke by decreasing the blood's clotting ability. Dipyridamole (Aggrenox, Persantine) is the combination of aspirin and extended-release dipyridamole, two antiplatelet/platelet aggregation inhibitors that prevent a future TIA or stroke. Heparin (Calciparine, Liquaemin), an anticoagulant drug, is sometimes used to reduce acute stroke damage or stroke risk in hospitalized patients and to lower the risk of blood clots forming in their leg veins. Ticlopidine (Ticlid), an antiplatelet, helps prevent another stroke. Tissue plasminogen activator (Activase) is a thrombolytic drug that lessens the severity of ischemic stroke if it is given within three hours of stroke onset. Warfarin (Coumadin) is an anticoagulant often prescribed for daily use to reduce the risk of stroke.

Cardiovascular disease is even more widespread in the U.S., with more than 81 million people having one or more forms of it.

Heart failure is the least common of the four types of cardiovascular disease. Like the other cardiovascular diseases, ACE inhibitors are employed to assist those with heart failure. Examples include enalapril (Vasotec), lisinopril (Prinivil, Zestril) and captopril (Capoten). Angiotensin II receptor blockers, or ARBs (like losartan [Cozaar] and valsartan [Diovan]) have many of the same benefits as ACE inhibitors, providing an alternative for people who don't respond well with ACE inhibitors. Aldosterone antagonists like spironolactone (Aldactone) and eplerenone (Inspra) are potassium-sparing diuretics that also help the heart pump more efficiently. They may reverse scarring of the heart and allow those with severe heart failure to live longer. Digoxin, or Lanoxin, as well as beta-blockers (such as carvedilol [Coreg], metoprolol [Lopressor] and bisoprolol [Zebeta]) and diuretics (bumetanide [Bumex] and furosemide [Lasix]) also are used for patients with heart failure.

Diabetes Medication

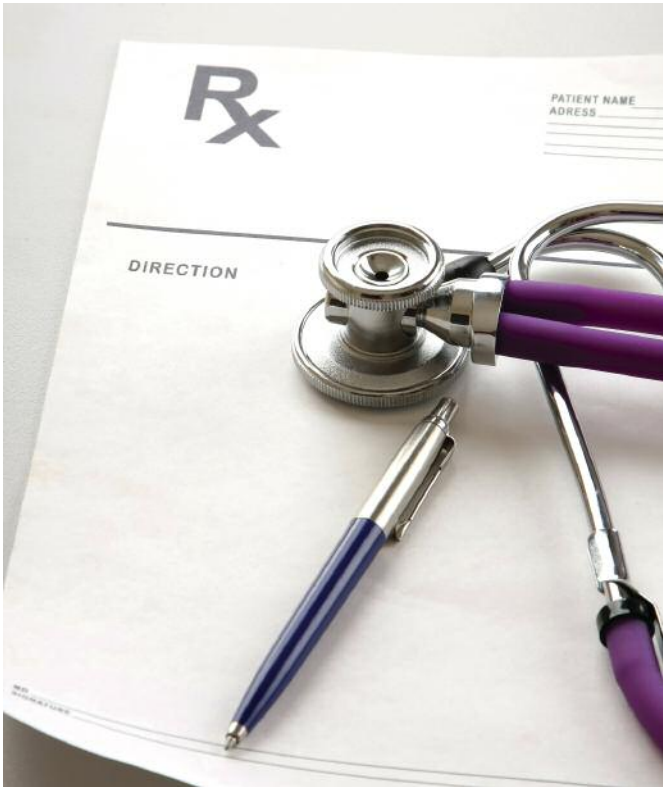
Due to the rise in the number of Americans with risk factors, such as excess weight, type 2 diabetes sufferers continue to increase as a percentage of the population — even as more lifesaving medications are being brought to market. Diabetes medication includes various types of insulin. Rapid-acting insulin — such as insulin lispro (Eli Lilly), insulin aspart (Novo Nordisk) or insulin glulisine (Sanofi-Aventis) — begins to work about five minutes after injection, peaks in an hour and continues to be effective for two to four hours. Regular- or short-acting insulin reaches the bloodstream within 30 minutes after injection, peaks after two to three hours and is good for three to six hours. Intermediate-acting insulin, which hits the bloodstream about two to four hours after injection, peaks four to 12 hours later and lasts for 12 to 18 hours. Long-acting insulin, which takes six to 10 hours to start working, lasts for 20 to 24 hours.

Insulin isn't the only injectable drug that is used to treat people with diabetes. Pramlintide (Symlin) is a synthetic form of the hormone amylin, which is produced along with insulin by the beta cells in the pancreas. It helps maintain normal blood glucose levels. Exenatide (Byetta) is the first in a new class of drugs for the treatment of type 2 diabetes called incretin mimetics. A synthetic version of the naturally occurring hormone exendin-4, exenatide lowers blood glucose levels by increasing insulin secretion.

There are six types of oral medications that can alleviate the effects of diabetes. Sulfonylureas (such as chlorpropamide [Diabinese], glipizide [Glucotrol and Glucotrol XL], glyburide [Micronase, Glynase, and Diabeta] and glimepiride [Amaryl]) and meglitinides (repaglinide [Prandin] and nateglinide [Starlix]) stimulate the pancreas' beta cells to release more insulin. Biguanides, like metformin (Glucophage), lower blood glucose levels by decreasing the amount of glucose produced by the liver. Thiazolidinediones (rosiglitazone [Avandia] and pioglitazone [ACTOS]) help insulin absorption in muscle and fats and also reduce glucose production in the liver. Alpha-glucosidase inhibitors assist the body in lowering blood glucose levels by blocking the breakdown of starches in the intestine and slowing the breakdown of some sugars. A new class of oral medications, DPP-4 inhibitors, improve A1C without causing hypoglycemia. Types like sitagliptin (Januvia) and saxagliptin (Onglyza) work by preventing the breakdown of a naturally occurring compound in the body called GLP-1.

Aspirin, which as mentioned earlier significantly lowers the risk of repeat heart attacks, also may benefit those with diabetes more likely to suffer from a heart attack. It addition, it can aid diabetes sufferers who already have had a heart attack or a stroke, or who have heart disease. However, the long-term benefits for aspirin use for this population are not yet known. For example, its effects have not yet been studied in people under age 30.

Aside from insulin, similar injectables and oral medication, people with diabetes have to take steps to prevent getting the



flu. According to the ADA, people with diabetes are about three times more likely to die from the flu and pneumonia. To lessen the risk, people with diabetes are advised by the ADA to receive flu shots each year and pneumonia vaccine as frequently as recommended by their physician.

The Evolution of Heart Disease Medication

The resounding success of Pfizer's Lipitor and the difficulty of topping the drug as the world's best-selling medicine have caused many drug companies to veer away from heart disease and focus their drug development efforts on other ailments. Even Pfizer itself has dropped heart disease on its list of priorities. Warfarin has been considered the primary blood thinner, but the recently approved dabigatran has emerged as a contender. Developed by Boehringer Ingleheim GmbH and marketed under the brand name Pradaxa, it has proved, according to the company, to be more effective than warfarin in preventing stroke in patients with atrial fibrillation. Johnson & Johnson has created its own answer to warfarin, rivaroxaban. The not-yet-approved medication is said to help prevent strokes and avoid bleeding complications in patients with atrial fibrillation. Going up against Pradaxa for anti-clotting are xarelto from Bayer and Johnson & Johnson and apixaban from Bristol-Myers Squibb and Pfizer. Merck's experimental pill, vorapaxar, is supposed to have the same effects as a blood thinner, lowering the risk of heart attack and stroke, but without excessive bleeding. Merck also is testing a pill called anacetrapid, a CETP inhibitor that is supposed to reduce bad (LDL) cholesterol by 40 percent and raise good (HDL) cholesterol by 138 percent.

AstraZeneca will challenge Plavix, the second-best-selling drug worldwide, with Brilique. The makers claim that studies show it more effectively cuts the risk of heart attacks, strokes and death linked to heart disease than Plavix. Brilique is set to be sold in the European Union later this year. While the FDA had delayed approval for the oral anti-platelet medication, which is to be marketed as Brilinta in the U.S., it is set to rule this summer on AstraZeneca's reapplication for the agent's approval. Another Plavix challenger is Novartis' and Portola's elinogrel, which is in final-stage testing. The experimental blood thinner was found to work quickly in patients who had surgery to unblock an artery.

Trials have just started in the United Kingdom for a daily polypill that is supposed to reduce the risk of heart attacks and strokes. Made by the India-based company Cipla, the polypill is a combination of five low-dose generic drugs. Since those five generic drugs are well-known and are usually prescribed with one another, it will likely be easier for makers to get the polypill on the market while also reducing costs for low-income patients in the U.S.

The Evolution of Anti-Diabetic Medication

Most of the new anti-diabetic medicines that have been coming out are for type 2 diabetes and they are once-a-week treatments instead of the traditional daily or twice-a-day options. Three long-acting glucagon-like peptide-1 receptor agonists, Eli Lilly's dulaglutide, GSK's albiglutide and Sanofi-Aventis' lixisenatide, are in Phase III testing. Roche's aleglitazar, a dual PPAR agonist, also shows promise for the management of cardiovascular disease in high-risk patients, though it must undergo testing.

There are four types of cardiovascular disease, each with its own set of medications.

A different kind of drug in Phase III trials is Bristol-Myers Squibb and AstraZeneca's dapagliflozin, a renal sodium-dependent glucose transport (SGLT-2) inhibitor, under devel-

opment for the treatment of type 1 and 2 diabetes. Glucose is usually removed from the bloodstream by glomerular filtration, but it's subsequently reabsorbed through active transport mechanisms in the proximal convoluted tubule. Tubular reabsorption is done by two sodium-glucose co-transporters, SGLT-1 and SGLT-2, with the latter accounting for about 90 percent. Reabsorption occurs in diabetic patients and healthy people, the opposite of what is needed, which is why inhibition of SGLT-2 reduces the risks associated with diabetes. Aside from helping patients lower blood sugar, SGLT-2 inhibitors also have been shown to help patients lose weight.

The Future of Treatment

A lot of work is left to be done to battle diabetes, both to prevent it and stop it, says Dr. Robert Henry, professor of medicine, Department of Medicine, Division of Endocrinology and Metabolism at the University of California, San Diego, and president, Medicine & Science of the ADA: "We'd love to have a world free of diabetes, but it's not happening. With our current changing lifestyles, I see the epidemic of diabetes escalating." He adds that it will take a major commitment to research in this area to effect major change.

Due to the rise in the number of Americans with risk factors, such as excess weight, type 2 diabetes sufferers continue to increase as a percentage of the population — even as more lifesaving medications are being brought to market.

"The positive side is that we've come a terrific long way," he says. "The downside is we have a long way to go for type 1 and 2 diabetes. But the goal is to stop the disease, and I think that's a reasonable goal. It's going to come in small steps. The most important thing is that we don't stop doing research — once we do that, we have no hope of those advances."

Dr. Harlan Krumholz, professor of cardiology, epidemiology and public health at the Yale University School of Medicine and AHA spokesman, strikes a similar note about heart disease treatments, saying that big strides have been made against heart disease, but that hard work lies ahead in future treatment. "I think we need to improve our systems of care," Krumholz says. "I still think there are ways to think we can do better, but the innovation has to be better than it has been in the past. The bar's been raised, the industry knows that. In order for it to be good, it has to be really good and safe."

Ironically, the strides that have been made in reducing risk factors make it harder to treat heart disease with medication, Krumholz says. "We recognize the success of lifestyle changes and lowering risk," he says. "The challenge of new medications is coming on top of that. Even if you have a significant reduction in risk, you'll have a harder time in gains. That raises the bar on the drugs; it makes it more difficult. You almost have to have a bigger impact to treat it because the overall numbers have gone down."

Striking a note that's both worrisome and promising about the possibilities still available for progress, Krumholz says that we still have a long way we can go in the treatment of heart disease. "It's a tribute to the companies and the profession that we made so much progress, but we're only halfway done with the success," Krumholz says. "At the end of the day, when the final story is told, we are more toward the beginning than we are toward the ending of fighting this disease." ❖

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Nuclear Accidents:

Determining Fukushima's Health Consequences

Despite international concern over Fukushima's nuclear accident, comparing it with the 1986 accident in Chernobyl reveals that immediate medical intervention is not needed. However, if it were, techniques are available to counteract the radiation's effects.

By Robert Peter Gale, MD, PhD

Twenty-five years ago, the Chernobyl nuclear power station in Ukraine exploded killing 31 people, contaminating substantial areas of Ukraine, Belarus and Russia and sending shock waves around the world. We now face another global nuclear event: a "meltdown" at reactors at the Fukushima Daiichi nuclear power station in Japan.

Although officials and the public prepared to face the worst, the major immediate consequences at Fukushima turned out to be political, psychological and economic — not medical. This is made evident by a comparison of it with the Chernobyl accident. However, had medical intervention been necessary, techniques similar to those employed in Chernobyl are available that can counteract the effects of radiation. And, despite the lack of need for immediate medical intervention in Japan, a medical strategy is being formed to deal with future accidents, even with the likelihood that one will never be needed.

Fukushima vs. Chernobyl: Reactors

There are substantial similarities and differences between the Chernobyl and Fukushima-type reactors. The Chernobyl reactor was a RBMK (bolshoy moshchnosty kanalny)-type boiling water reactor with a graphite moderator. Because of its huge size, it was not possible to place it within a containment structure. RBMK-type reactors can produce weapons-grade plutonium, as well as electricity, which accounts for their large size.

The Fukushima units also are boiling water reactors but are much smaller, cannot produce weapons-grade plutonium (they do produce some plutonium as a consequence of fissioning uranium) and are within two containment structures: a steel vessel and a secondary containment building. And, although there are several other important technical differences between these reactors, they need not concern us here.

When comparing the Chernobyl and Fukushima accidents, several key variables need to be considered: 1) how much fuel is contained in the reactor; 2) what type of fuel it is: uranium or a mixture of uranium and plutonium; 3) how much of the fuel is expended; 4) how much radiation is released from the reactor core; 5) what are the physical-chemical forms of the released radionuclides; and 6) how much of the released radiation enters the environment where it affects biota, including humans.

Fukushima vs. Chernobyl: Health Consequences

When estimating the potential health consequences of radiological releases at Fukushima versus Chernobyl, fundamental differences in containment and the amount of radiation released are key. Because the Chernobyl reactor core was not in a containment structure and because the reactor had recently been refueled, a tremendous amount of radiation was released into the environment: Predominately 131-iodine and 134- and 137-cesium (but also 90-strontium and 239-plutonium) were ejected into the lower troposphere and were spread by winds throughout the Northern Hemisphere (winds of the hemispheres do not mix). Rain was important in depositing the airborne radiation within the nuclear cloud throughout northern Europe. Eventually, the radioactive cloud reached the U.S.

This Northern Hemispheric dispersion of radionuclides led to health consequences that were most easily detected in Ukraine, Belarus and Russia, where about 8,000 excess cases of thyroid cancer were detected, predominantly among young persons. These thyroid cancers were caused by 131-iodine in milk and dairy products (137-cesium also may have contributed). However, it is equally important to recall that there is, as yet, no convincingly documented substantial increase in leukemia or other cancers at 25 years post-accident. This is an adequate observation period for leukemias, but it is incomplete for solid cancers. Because leukemias are a harbinger of other cancers, the absence of a substantial increase in leukemia risk is encouraging. If we use data of cancer risk derived predominately from the atomic bomb survivors, we would estimate 2,000 to 15,000 excess cancers over 50 years following the accident. This magnitude of increase is difficult to detect in the context of more than 40 million expected cancers in Europe and the ex-Soviet Union in this interval. Other concerns like genetic abnormalities and birth defects have, fortunately, not materialized. But there are many collateral effects including the evacuation and relocation of about 300,000 people.

Although officials and the public prepared to face the worst, the major consequences at Fukushima turned out to be political, psychological and economic — not medical.

These data estimates can be used to make some estimates of likely health consequences from the Fukushima nuclear accident. Assuming there is no further radionuclide leakage, the Fukushima accident has released about 10 percent as much 131-iodine and 137-cesium as the Chernobyl accident. Also, the dispersion of the release is far less than Chernobyl. Finally, in contrast to Chernobyl, it has been possible to restrict consumption of contaminated milk and dairy products and to distribute nonradioactive iodine (potassium iodide) to block uptake of 131-iodine. Based on these considerations, we might expect few if any cases of thyroid cancer and about 200 to 1,500 leukemias and other cancers combined over the next 50 years. During this interval, about 20 million Japanese will develop cancer unrelated to Fukushima. Thus, the attributable risk of cancer from Fukushima should be less than 0.1 percent. This is, obviously, below our level of detection in epidemiological studies. Raising the price of a pack of cigarettes in Japan by 10 percent to 20 percent would result in a much greater reduction in cancer risk than the increase we can predict from the Fukushima accident. Another consequence of the accident is that about 120,000 people have been displaced, but many may be able to return within one to two years, if not sooner.

Because the Fukushima nuclear reactors are smaller, they are housed within two containment structures, and with the small amount of radiation released during the accident, the major health consequences are not medical.

The Chernobyl nuclear ractor was too large to be placed inside a containment structure, causing the release of significantly more radiation during the accident 25 years ago compared with last year's Fukushima nuclear accident.

Fukushima vs. Chernobyl: Medical Intervention

At Chernobyl, the use of advanced medical techniques like sophisticated antibiotics and antivirus drugs, transfusions of blood components, genetically engineered hormones and bone marrow transplants were used to treat acute radiation syndrome. These types of techniques save about 85 percent of persons exposed to more than 1 gray (a unit of absorbed radiation dose of ionizing radiation) of acute whole-body radiations. This has led to recommendations for a medical strategy to deal with future nuclear accidents. Fortunately, there has been no need to test these recommendations until now. No worker, so far, at Fukushima has received a radiation dose greater than 170 mSv (the derived unit of dose equivalent radiation).

However, if there had been a need for a medical response at Fukushima, it is important to understand how medical techniques work to counteract radiation's effects. There are three types of high-dose acute radiation syndromes: gastrointestinal, bone marrow and central nervous system. From a medical intervention perspective, bone marrow effects are the most important, and prompt, effective actions can save lives. People with gastrointestinal acute radiation syndrome will usually recover, whereas those with central nervous system effects will usually die.

Gastrointestinal. The effects of gastrointestinal radiation syndrome — nausea, vomiting and diarrhea — usually are treated symptomatically and with fluid replacement. It can be treated with molecularly cloned hormones, which accelerate recovery of the damaged cells of the gastrointestinal system; however, this treatment has not yet been tested in radiation accident victims. In addition, there are some recently developed drugs intended to mitigate radiation damage to the gastrointestinal tract when taken soon after radiation exposure, but whether these will work in an accident setting is unknown.

There are three types of high-dose acute radiation syndromes: gastrointestinal, bone marrow and central nervous system.

Bone marrow. Serious suppression of bone marrow function can cause bleeding, infection or both and can result in death within three to six weeks. Bone marrow suppression occurs at doses exceeding 1 to 2 gray. But bone marrow replacement may be needed after exposures exceeding 8 to 10 gray. Acute exposures exceeding 15 gray result in immediate symptoms, such as confusion, and then death from effects to the central

nervous and cardiovascular systems. Because of the lethal consequences, the medical community's focus is on mitigating the suppression of bone marrow function.

The medical approach to radiation-induced bone marrow failure is determined by the severity and the estimate of how long the blood cell production will decrease, including red blood cells (needed for oxygen transport), white blood cells (needed to prevent infections) and platelets (needed to prevent bleeding).

To respond to deficient bone marrow production of red blood cells — and to ultimately stimulate the production of these cells — cloned hormones can be used. It is more difficult to correct a reduced production of white blood cells, specifically granulocytes (needed to prevent bacterial and fungal infections). Antibiotics and antifungal drugs are typically given to prevent or treat infections. Ionizing radiation also can activate latent infections of DNA viruses, especially herpes viruses and cytomegalovirus; antiviral drugs, or sometimes antibodies, can be administered in such cases. In some accidents, intravenous immune globulin also is given to prevent or moderate infections. When platelet production is reduced, platelet transfusions and cloned hematopoietic growth factors, which stimulate platelet production, can be used.

Central nervous and cardiovascular systems. There is no effective medical intervention for these serious consequences of very high-dose acute radiation exposures. Though sedation and cardiovascular support are given, most victims die soon after exposure.

Fukushima vs. Chernobyl: Lessons Learned

The global concern over these accidents makes it clear that policymakers and the public should be educated on what radiation from an accident at a nuclear power station can and, more importantly, cannot do. For example, in the short-term, it is almost better to remain at one's home or office (shelter-in-place) than to evacuate. And, people should be made aware not to buy or take iodine tablets unless instructed by public health officials or their physician to do so. Response to such an event requires a solid, well-informed command-and-control structure and a panel of credible, independent medical experts to provide information and instructions to the public in settings where government credibility is often severely compromised.

Most accidents at nuclear plants involve few workers. There are extensive guidelines for dealing with these incidents that work reasonably well. There also are well-established command-and-control procedures and experienced personnel who rehearse potential incidents. Unfortunately, the high standards, at least on paper, in most developed countries like Japan may not apply to all nations, especially in developing countries, where many nuclear plants plan to be, or are currently being, developed (like China and Indonesia). Because "an accident anywhere is an accident everywhere," developed countries should offer expert medical and accident planning advice to their neighbors. This is being done by the International Atomic Energy Agency. As always, prevention of accidents at nuclear power stations is preferred to medical interventions.

As we have seen in Japan, a major natural disaster can disrupt the safety measures at almost all nuclear power stations.

The major issues with an event at a nuclear plant for the public are usually political, psychological and economic — rather than medical. As we have seen in Japan, a major natural disaster can disrupt the safety measures at almost all nuclear power stations. Are there adequate numbers of trained emergency personnel at nuclear power plants, especially those in geographically and/or politically unstable regions? In earthquakes of extraordinary magnitude, the widespread destruction, floods or tsunamis, fires and loss of life make the potential effects of a radiation release of less real impact.

Emergency Preparedness Is Key

Because of the recent accident at Fukushima, there is renewed concern regarding potential accidents at nuclear power stations. Dealing effectively with these concerns requires diverse strategies, including policy decisions, public education and, as a last resort, a medical response. It is important to keep long-term risk-benefit ratios in mind. As alarming as the news sounds, there are unlikely to be major health consequences of current events at nuclear power stations in Japan. And, we should not let one event, no matter how dramatic, alter our long-term calculus. On the other hand, we clearly need to increase our emergency preparedness at nuclear power stations if we want public acceptance of continued use or expansion of nuclear energy. Needless to say, accident prevention is key. ❖

ROBERT PETER GALE, MD, PHD, *is a physician and scientist, and medical director of NuFACTOR, the specialty pharmacy of FFF Enterprises Inc. He led the international medical team responding to the Chernobyl accident and is now at Fukushima. He also develops new cancer drugs and teaches in Los Angeles and London.*

The Role of Less-Common Hyperimmune Globulins

The use of the less-common hyperimmune globulins is rare, but as three cases describe, they are lifesaving.

By E Richard Stiehm, MD

The hyperimmune human immunoglobulins (IGs) are high-titered IGs derived from the plasma of immunized or convalescing donors, and are used for prevention or treatment of infectious diseases for which standard IGs are of little or no value. There are five widely used hyperimmune globulins: tetanus IG (TIG), rabies IG (RIG) hepatitis B IG (HBIG), cytomegalovirus IG (CMV-IGIV) and Rh IG (RhIG), as well as three less commonly used hyperimmunes — botulism IG (BIG), varicella-zoster IG (VZIG) and vaccinia IG (VIG) — none of which is available in hospital pharmacies. All three of the less-common hyperimmunes must be obtained by special requests from an authorized distributor or from the U.S. Centers for Disease Control and Prevention (CDC). Their use and how to obtain them is reviewed in the *Red Book of the American Academy of Pediatrics*, which is available online,[1] as are detailed references.[2]

This article illustrates the use of the three less-common hyperimmunes in three clinical vignettes.

Case 1: An Infant with Progressive Weakness

Rachael, 6 months old, was a healthy and happy term infant who became unusually listless and quiet. She had just been switched from breast to bottle feeding and was drinking well from the bottle. But then, her abdomen became distended, she was constipated and was feeding poorly. When she started choking on her bottle, she was rushed to the emergency room and admitted. By then, she was breathing poorly, refusing all feedings, and was unable to hold her head up. She was placed on a respirator, and tube feedings were started.

The parents were told that Rachael would need care in the intensive care unit for several months, but that she should recover completely if a stool test confirmed a diagnosis of infant botulism. The doctor got on the phone and had a 2 mL vial of botulism IG delivered within 24 hours. It was given intravenously over three hours. Rachael remained hospitalized for 48 days, but recovered completely.

Botulism Immune Globulin (BIG)

BIG, aka BabyBIG, is used to treat infant botulism. Despite its high price tag, BabyBIG is cost-effective because it markedly shortens the length of hospitalization for an affected infant.[3]

Botulism is a severe paralytic poisoning due to absorption of botulinum toxin from a wound or mucous surface. It can result from ingestion of toxin in contaminated canned goods (food botulism), from direct toxin entry into open wounds or by skin popping with unsterile needles by drug addicts (wound botulism), or from ingesting botulinum spores in food (infant botulism). Since botulism spores are ubiquitous in the soil, they are present in many foods, including honey and corn syrup used in infant formula.

None of the three less-common hyperimmune globulins is available in hospital pharmacies.

In infant botulism, the ingested spores multiply in the immature gastrointestinal tract and, after an incubation period of three to 30 days, begin to produce botulinum toxin. The absorbed toxin causes gastrointestinal stasis and peripheral muscle paralysis.[4]

Most affected infants are breast-fed infants less than 6 months of age who have just started formula feeding. They present with a poor suck, a weak cry, abdominal distention, constipation and gradual onset of muscle weakness and respiratory paralysis. They require meticulous care, often as long as six months. BabyBIG shortens infants' hospitalization and results in an average savings of $80,000 of hospital care.[3]

The need for a human botulinum antibody was recognized as early as 1976 because of the serious side effects and short half-life of the existing equine antitoxin.[5] In 1986, the U.S. Army developed a human botulism IG, but a proposed 1990 trial was postponed because of its possible need in the 1990 Persian Gulf War. This development led the California Department of Health Services (CDHS) to recruit donors who had received an experimental botulinum toxoid vaccine 30 years ago. And, these recipients, together with other immunized donors, volunteered their plasma for a new BIG for intravenous use manufactured by the Massachusetts Public Health Laboratories as a public service.[5]

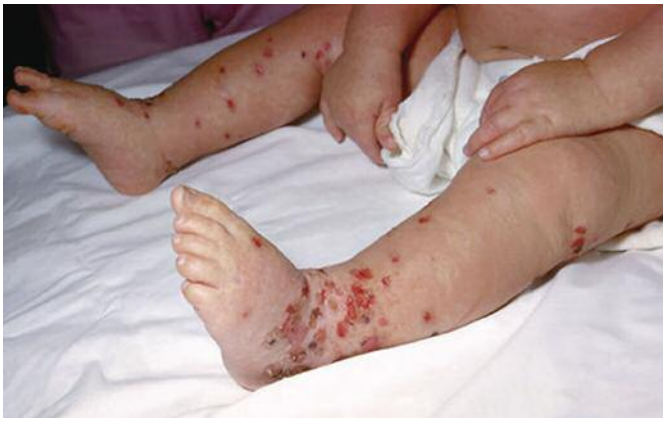
In 1992, Dr. Steve Arnon of the CDHS organized the pivotal five-year controlled clinical trial involving 120 patients at 59 sites. After an additional open label trial, BabyBIG was licensed in 2003.[4] These trials were supported by the state of California and the Office of Orphan Drug Development of the U.S. Food and Drug Administration.

BIG-Intravenous (human) (BIG-IV), its official name, is manufactured as a 5% solution in 2 mL vials. The current dose is 50 mg/kg, but that varies with the titer of the antibody in each lot.

It is estimated that there are 250 cases of infant botulism in the U.S. every year of which only 100 are identified and treated. Infant botulism has been recognized in many other countries but the diagnosis is often overlooked. The 24-hour hotline to the California Department of Health Services is (510) 231-7600 for drug availability and current dosage.[1]

Case 2: A Boy with a Recent Progressive Skin Rash

Jon, an 18-month-old boy, developed infantile eczema starting at 3 months of age. The itchy rash of the face, elbows and ankles prevented him and his mother from getting a good night's sleep. A combination of antihistamines, antibiotics and local corticosteroid cream resulted in good control of the rash except for a few scattered areas on the legs.



Jon's father was at an Army base in training for deployment to Iraq. He received a smallpox vaccine one week before a home visit, and when he arrived home, he had a healing pustule on his upper arm.

Six days after his dad's arrival, Jon developed a weeping eruption on both ankles. The parents thought his eczema had returned, so they applied a steroid cream, which made the skin worse. When Jon developed a fever, he was taken to his pediatrician, who diagnosed eczema vaccinatum. He promptly called the CDC for Vaccinia IG. Jon required two doses over three days before healing ensued.

Vaccinia Immune Globulin (VIG)

Vaccination against smallpox (variola) utilizes a live strain of cowpox virus (vaccinia). Following vaccination, the recipient develops neutralizing antibodies that cross-react with smallpox virus to provide long-term immunity.

Following an international vaccine program, smallpox was eradicated from the world in 1979. The virus still exists in government laboratories in the U.S. and Russia (and possibly other countries), and is a potent biological weapon against an unimmunized population. Therefore, the military and laboratory personnel working with vaccinia virus are still vaccinated.

Serum from vaccinated cows was used as early as 1895 to protect against smallpox. Henry Kempe, an American pediatrician working in India in the 1960s, demonstrated that IG from vaccinated subjects protected recently exposed unvaccinated household contacts against smallpox.[6]

The main use of VIG is in the treatment of complications following smallpox vaccine or, less commonly, vaccinia in close contact.[7] These complications include eczema vaccinatum, generalized vaccinia, vaccinia gangrenosum (progressive spread from the vaccine site), vaccinia encephalitis and vaccinia keratitis of the eye. As in Jon's case, spread to household contacts also may occur, particularly if the contact has eczema or another chronic skin disorder. The most severe and sometimes fatal complications have occurred in immunocompromised subjects, which included infants with unrecognized immunodeficiencies when smallpox vaccine was given routinely.

All these complications (except for vaccinia keratitis) are indications for VIG. The CDC maintains a Smallpox Vaccine Adverse Events Clinical Information line at (877) 554-4625 for information and obtaining VIG.[1]

The existing products are made by Cangene of Canada and Dynport of the U.S. for either intravenous or intramuscular use. The U.S. military is stockpiling a supply of both VIG and vaccine for defense against biological warfare.[8]

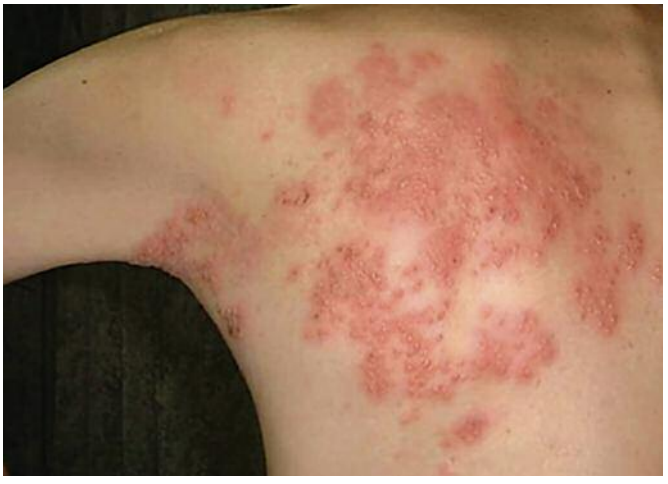
Case 3: A Pregnant Woman Exposed to Shingles

Anna was 32 and wanted to start a family. She had never had chickenpox (varicella) or varicella vaccine. Her obstetrician confirmed that she was seronegative (susceptible) to varicella, but he did not give Anna varicella vaccine.

Three months later, when Anna was 10 weeks pregnant, her mother visited complaining of pain behind one ear. When Anna pulled back her mother's hair, she noted many small vesicles. An internist confirmed that the painful rash was shingles.

Despite BabyBIG's high price tag, it is cost-effective because it markedly shortens the length of hospitalization for an affected infant.

Anna immediately contacted her obstetrician about this exposure. On the advice of an infectious disease consultant, the obstetrician did not give varicella-zoster IG (VZIG) or acyclovir. Anna's baby was born at 35 weeks with congenital varicella syndrome with club feet, a heart abnormality, swallowing problems and mental retardation.



A lawsuit against the obstetrician and his consultant was filed for failure to give the vaccine before pregnancy and failing to give VZIG during pregnancy to prevent congenital varicella. It settled for the maximum of the physician's malpractice insurance.

Varicella-Zoster Immune Globulin (VZIG)

Varicella (chickenpox) is a considerable risk for susceptible immunosuppressed patients. These include patients with leukemia, particularly children, patients on immunosuppressive drugs and patients with cellular immunodeficiencies.

Although regular IG does not prevent chickenpox in exposed susceptibles, Ross et al. in 1962 showed that IG modifies its severity.[9] These results led to trials of high-titered antibody from patients convalescing from herpes zoster given as plasma (zoster immune plasma) or IG (zoster IG). Both products prevented varicella in exposed susceptible high-risk children.

Because of the limited supply of plasma from convalescing zoster patients, the product is now prepared from normal plasma selected for high titers of varicella antibody and is termed VZIG.[10] VZIG will prevent or reduce complications resulting from varicella infection in exposed susceptible patients who have not had varicella vaccine, as well as patients with a compromised immune system as a result of disease or age. These include immune-compromised adults and children, full-term infants less than 1 year of age, healthy non-immune adults, newborns of mothers with chickenpox, premature newborns and pregnant women. The latter are susceptible to varicella pneumonia and/or transmission of varicella to their fetus. There is compelling evidence that the use of VZIG in early pregnancy reduces the likelihood of devastating congenital varicella syndrome.[11]

The Massachusetts Public Health Department produced VZIG until 2006. A new product, VariZIG, manufactured by Cangene, is available under an investigational new drug protocol through the sole U.S.-authorized distributor, FFF Enterprises Inc. Its toll-free number is (800) 843-7477.[1]

VariZIG is supplied as 125 U vial reconstituted to a 5% solution. The dose is 125 U/10 kg with a maximum dose of 625 U. This product is for intramuscular use.

Standard intravenous IG (IVIG) at 400 mg/kg has been recommended when VariZIG is unavailable.

A Look to the Future

Fortunately, hyperimmune globulins are available for certain less-common diseases, many of which may be lethal without their use (e.g., newborn botulism, generalized vaccinia).

For the future, novel uses for existing products are being studied, such as for prevention of congenital cytomegalovirus infection with CMV-IGIV, and prevention of reinfection following liver transplantation for hepatitis B with HB-IGIV.[2]

In addition, new antibody products are under development for emerging infections, such as West Nile virus and hepatitis C, and for bioterrorism organisms, such as anthrax.

And last, monoclonal antibodies for several infections (staphylococcus, influenza) also are being developed. ❖

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References

1. Pickering, LK, Baker, CJ, Kimberlin, DW, Long, SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2009, 984 pages.
2. Stiehm, ER, and Keller, MA. Passive Immunization in Feigen, RD, Cherry, JD, Demmler-Harrison, GJ, and Kaplan, SL. *Textbook of Pediatric Infectious Diseases*, 6th ed. Saunders/Elsevier, Philadelphia, 2009, pp 3401-3446.
3. Underwood, K, Rubin, S, Deaker, S, et al. Infant botulism: A 30 year experience spanning the introduction of botulism immune globulin intravenous in the intensive care unit at Childrens Hospital Los Angeles. *Pediatrics*, 2007, 120: e1380-5.
4. Arnon, SS, Schechter, R, and Maslanka, SE. Human botulism immune globulin for the treatment of infant botulism. *New England Journal of Medicine*, 2006, 354:445-7.
5. Arnon, SS. Creation and development of the public service orphan drug human botulism immune globulin. *Pediatrics*, 2007, 119:785-789.
6. Kempe, CH, Bowles, C, Meiklejohn, G, et al. The use of vaccinia hyperimmune gamma globulin in the prophylaxis of smallpox. *Bull World Health Organ*, 1961, 25:41-48,
7. Kempe, CH. Studies on smallpox and complications of smallpox vaccination. *Pediatrics*, 1960, 26: 176-89.
8. Witte, KR. Vaccinia immune globulin: Current policies, preparedness and product safety and efficacy. *International Journal of Infectious Diseases*. 2006, 10:193-201.
9. Ross, AH. Modification of chickenpox in family contacts by administration of gamma globulin. *New England Journal of Medicine*, 1962, 267:369-76.
10. Orenstein, WA, Heymann, DL, Ellis, RJ, et al. Prophylaxis of varicella in high risk children: Dose response effect of zoster immune globulin. *Journal of Pediatrics*, 1981, 98:368-73.
11. Cohen, A, Moschopoulos, P, Stiehm, RE, et al. Congenital varicella syndrome: The evidence for secondary prevention with varicella-zoster immune globulin. *Canadian Medical Association Journal*, 2011, 183: 204-8.

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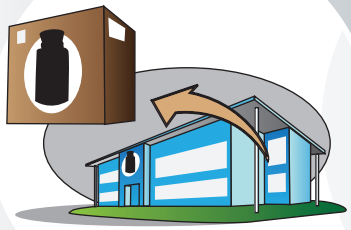

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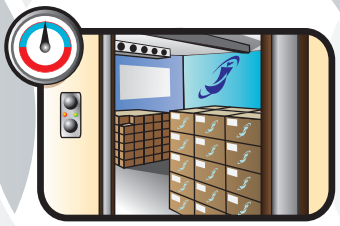

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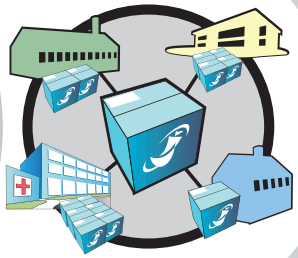

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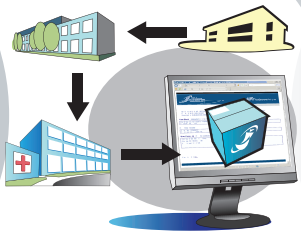

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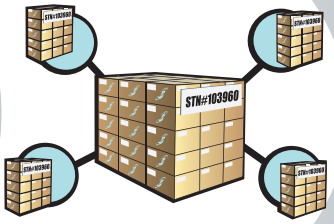

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A WORLD WITHOUT VACCINES

Imagine a plague that wipes out the entire population of Chicago. Implausible? Without vaccines, that's the number of people — three million to be specific — who would die each year from vaccine-preventable diseases.

By Trudie Mitschang

A young girl gasps desperately for air, her face contorted and purple as a distinctive whooping sound emits from her severely restricted airways. A once-active toddler stares blankly at the ceiling with only his head protruding from a cylindrical metal container — the "iron lung" where he will spend the rest of his short life. Elsewhere, an entire town succumbs to a deadly infection that begins with a high fever and leaves its victims covered in painful pustules; those who survive remain permanently disfigured. These images may sound like plots from an apocalyptic movie, but the reality is these scenes represent a snapshot of world history. As recently as a century ago, vaccine-preventable diseases like pertussis (whooping cough), polio and smallpox ran rampant in big cities and small towns alike. Literally no one was immune, since vaccines for these infectious maladies had yet to be invented. It was a world without vaccines — a time vastly different from the world we live in today.

It's been said that those who cannot remember the past are condemned to repeat it. For many in the industrialized world, horrific diseases such as these seem obscure and unreal — the lore of times gone by. It could be described as a situation where lack of familiarity breeds complacency; if you've never seen someone crippled by polio, perhaps it's not a real threat. This false sense of security has public health experts worried. Are we looking at a future generation doomed to relive its disease-ridden past?

What a Difference a Century Makes

In the early 1900s, life in the United States bore little resemblance to today. There was no Internet, email or Facebook. U.S. roads were populated by a mere 8,000 cars, and only one in 14 homes even had its own bathtub. Birth control was nonexistent, and more than 95 percent of all births in the U.S. took place at home.[1] As a result, families tended to be larger, and for good reason, but many children did not survive past the age of 5. The U.S. infant mortality rate was a shocking 20 percent, and the childhood mortality rate prior to age 5 matched it at 20 percent.[2] While it can be argued that healthcare standards were far from what they are today, these dismal statistics were frequently the result of common childhood killers such as measles, diphtheria and smallpox. Today, many of these devastating diseases have been contained, thanks to the development and distribution of safe, effective and affordable vaccines.

Paul Roumeliotis, MD, Medical Officer of Health at the Eastern Ontario Health Unit, stated the following in his article Should My Child Be Vaccinated: "Vaccines have proven extremely effective in controlling and even eradicating some major childhood diseases. Indeed, smallpox — a severe and often fatal disease, which used to be common among children — has been entirely wiped out by worldwide immunization."[3]

When it comes to saving lives, vaccines have been called the most transformative public health achievement of our time. Routine vaccination programs have prevented the deaths of hundreds of millions of people and saved billions of dollars in public health expenditures. Yet in recent years, the contribution vaccines have made to public health has been questioned and even criticized. The reasons behind the backlash are complex, but one contributing factor may be that people simply don't remember what the world was like when vaccines were not yet available.

It's been said that those who cannot remember the past are condemned to repeat it.

Life Before Vaccines

In the 21st century, certain diseases like cancer, acquired immune deficiency (AIDS) and Alzheimer's are universally recognized and feared. But 100 years ago, a very different lineup of illnesses were considered the most fearful and potentially deadly:[4]

• *Smallpox*: This is a contagious, disfiguring and often deadly disease that has affected humans for thousands of years. Naturally occurring smallpox was eradicated worldwide by 1980. Before vaccines, smallpox was responsible for an estimated 300 million to 500 million deaths in the 20th century alone, more than double the number of people killed during the wars of that same period.

• *Measles*: Far more contagious than smallpox, measles can cause deafness, blindness, encephalitis and death. Between 2000 and 2007, measles deaths dropped by 74 percent worldwide. However, more than 18 million people continue to be infected by measles each year, resulting in 197,000 deaths in 2007, primarily among children. Before measles immunization was available, nearly everyone in the U.S. got measles. An average of 450 measles-associated deaths were reported each year between 1953 and 1963.

The iron lung — the first modern and practical respirator — was first used in 1928 to treat infantile paralysis caused by polio.

• *Polio*: In the years following World War II, polio was the most feared disease among parents in the U.S. Before polio vaccine was available, 13,000 to 20,000 cases of paralytic polio were reported each year in the U.S. These annual epidemics of polio often left thousands of victims — mostly children — in braces, crutches, wheelchairs and iron lungs.

Even with the vaccine backlash today, vaccination is considered a routine medical intervention.

• *Haemophilus influenzae type b (Hib)*: This serious disease is caused by bacteria. Before Hib vaccine became available, Hib was the most common cause of bacterial meningitis in U.S. infants and children, and there were approximately 20,000 invasive Hib cases annually. Hib meningitis once killed 600 children each year and left many survivors with deafness, seizures or mental retardation.

• *Rubella (German measles)*: Although rubella is a mild childhood illness, it can cause severe birth defects in children born to mothers who contract the disease in the early stages of pregnancy. The introduction of a rubella vaccine in 1969 has greatly reduced the incidence of congenital rubella syndrome (CRS) in the developed world, but the disease still causes approximately 110,000 cases worldwide each year. Before rubella immunization was used routinely in the U.S., there was an epidemic of rubella that resulted in an estimated 20,000 infants born with CRS, with 2,100 neonatal deaths and 11,250 miscarriages. Of the 20,000 infants born with CRS, 11,600 were deaf, 3,580 were blind, and 1,800 were mentally retarded.

• *Diphtheria*: This disease was once one of the most common causes of death in children. While it is now rare in the U.S., diphtheria is re-emerging in some areas of the world and is responsible for about 5,000 deaths each year in developing countries, primarily among children. Before diphtheria immunization was available in 1921, 206,000 cases and 15,520 deaths were reported. With vaccine development in 1923, new cases of diphtheria began to fall in the U.S., until in 2001, only two cases were reported.

• *Pertussis (whooping cough)*: This disease causes spasmodic, uncontrollable coughing that persists for weeks. Although global rates have fallen significantly since the arrival of the vaccine, pertussis still kills almost 300,000 people annually. Recent outbreaks of pertussis are thought to be related to parental resistance to immunization. Before pertussis immunization was available, nearly all children developed whooping cough. In the U.S., prior to pertussis immunization, between 150,000 and 260,000 cases of pertussis were reported each year, with up to 9,000 pertussis-related deaths.

Vaccines: A Brief History

Although the earliest smallpox vaccine was developed in 1796, widespread vaccination remained sporadic until the 20th century. The golden age of vaccine development began following World War II, when several new vaccines were developed in a relatively short period of time. Their success in preventing diseases such as polio and measles was considered revolutionary, and large-scale vaccination campaigns soon followed.

Even with the vaccine backlash today, vaccination is considered a routine medical intervention. But decades ago, vaccinating various population groups was a daunting task, requiring tremendous push and collaboration on the part of scientists, manufacturers, public health officials and government agencies. Following such efforts, success depended largely on a skeptical public's willingness to actually show up and get vaccinated. Still, when efforts were successful, results were dramatic. In 1967, for example, the World Health Organization (WHO) spearheaded a massive immunization campaign against smallpox. Just 10 years later, a disease that had plagued mankind for thousands of years had been virtually eliminated. Wild-virus polio, a disease that once circulated globally, is now present in only a handful of countries, and no cases have been diagnosed in the U.S. since 1979. Measles, mumps, rubella, diphtheria and pertussis were also reduced from epidemic ranges to contained outbreaks within a matter of a few decades.

The Success Paradox

A generation ago, childhood vaccination was considered a normal rite of passage. Today, many take for granted that children will be born and raised without the threat of paralysis, brain damage, blindness and death associated with childhood disease.

Over the years, diminishing outbreaks of once-terrifying diseases also have decreased the fear associated with them. Public awareness regarding the value of vaccines has begun to fade. As infectious disease rates fell, concerns began to grow over vaccine risks and side effects, which led some to question the wisdom of mass vaccination. This public scrutiny did lead to some positive outcomes, including improved oversight of vaccine manufacturing processes and better vaccine technology. The irony is, current vaccines are safer than ever before, yet more and more people question their efficacy. Because people do not fear diseases as they used to, vaccine rates have dropped in many regions, causing many once-eradicated diseases like measles and pertussis to stage unwelcome comebacks.

As of this writing, the U.S. is experiencing the highest number of measles cases in 15 years, according to a recent report by the Centers for Disease Control and Prevention (CDC). Between 2001 and 2008, the median number of cases has been 56 per year. By May 20, 2011, that number had more than doubled.[5] Additionally, documented cases of pertussis are on the rise. In 2010, California faced the state's biggest outbreak of pertussis since 1958, with public health officials declaring it an epidemic.[6] In early 2011, the CDC issued a health alert when the outbreak spread to other parts of the country.

The Indiscriminate Nature of Disease

Vaccine-preventable diseases are equal-opportunity attackers, affecting people from all walks of life. A look back in history shows some very well-known people whose lives were changed because a vaccine was either refused or simply not available:[7]

• Princess Alice of Hesse, a daughter of Queen Victoria, died of diphtheria in 1878 at age 35; her daughter Princess Marie had died of it a few weeks prior.[8]

• Benjamin Franklin was initially against vaccination but became an advocate after his unvaccinated 4-year-old son died of smallpox. It was recorded in his autobiography that he bitterly regretted not vaccinating his child.

• Thomas Jefferson's daughter Lucy died of whooping cough at the age of 2.

• In 1850, Abraham Lincoln's 3-year-old son died of diphtheria. In 1904, the daughter of President Grover Cleveland died of the same disease. The diphtheria vaccine became available in 1923.

• Franklin D. Roosevelt, president of the United States from 1933 to 1945, was a wheelchair-bound polio victim. The first polio vaccine became available in 1955.

• In 1962, a measles infection killed the 7-year-old daughter of Roald Dahl, the author of *Charlie and the Chocolate Factory*. Dahl later became a strong supporter of vaccines.

The above cases just highlight that these infections could affect almost anyone and that the vaccination debate has been around as long as many of the diseases themselves.

A World at Risk

Vaccine research and innovation is a rapidly developing field. It is anticipated that in the next decade and beyond, many conceptual and scientific advances will provide extraordinary opportunities to expand our current portfolio of immunizations. Major efforts are under way to develop new vaccines against pneumonia, HIV, tuberculosis, malaria and diarrheal diseases like rotavirus. Vaccines such as these obviously have the potential to save millions of lives. Without them or their predecessors that paved the way for current vaccine development, the world our children inherit could be a vastly different and more dangerous place.

The irony is, current vaccines are safer than ever before, yet more and more people question their efficacy.

WHO compares vaccination to clean water in terms of its ability to reduce the spread of infectious diseases. Few of us in the U.S. can envision life without access to clean drinking water; perhaps a paradigm shift is required to begin to view life without preventive vaccines in the same light. The benefits of vaccination extend far beyond individual or even community health and well-being. Reducing global infant mortality rates is a moral obligation for those in developed countries, and a major public health concern now and for the indefinite future. ❖

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

References

1. Rense.com. 100 Years Ago in America. Accessed at www.rense.com/general70/100yrs.htm.
2. Meckel, RA. "Levels and Trends of Death and Disease in Childhood, 1620 to the Present," in *Children and Youth in Sickness and Health: A Handbook and Guide*, ed. Golden, J, Meckel, RA, and Prescott, HM. Westport, Conn.: Greenwood Press, 2004, 3–24. Accessed at content.healthaffairs.org/content/24/3/611.full#R1.
3. ProCon.org. Should Any Vaccines Be Required for Children? Accessed at vaccines.procon.org/view.answers.php?questionID=001606.
4. Centers for Disease Control and Prevention. What Would Happen If We Stopped Vaccinations? Accessed at www.cdc.gov/vaccines/vac-gen/whatifstop.htm.
5. Centers for Disease Control and Prevention. Measles — United States, January-May 2011. Accessed at www.cdc.gov/mmwr/preview/mmwrhtml/mm6020a7.htm?s_cid=mm6020a7_w.
6. Gever, J. Pertussis Threat in California, MedPage.com. Accessed at www.medpagetoday.com/InfectiousDisease/GeneralInfectiousDisease/20861.
7. Iannelli, V. The History of Vaccine Preventable Illness. About.com. Accessed at pediatrics.about.com/od/immunizations/a/408_vac_history.htm.
8. Who is a famous person who died from Rabies? Answers.com. Accessed at wiki.answers.com/Q/Who_is_a_famous_person_who_died_from_rabies#ixzz1UlDc6YIr.

Myths and Facts: Fibromyalgia

Misconceptions about fibromyalgia have thrived since the early 1800s, but today it is recognized as a medical condition that is becoming more widely accepted and understood.

By Ronale Tucker Rhodes, MS

According to the Old Testament, Job described physical anguish that bore the same symptoms of what, today, is known as fibromyalgia: "I, too, have been assigned months of futility, long and weary nights of misery. When I go to bed, I think, 'When will it be morning?' But the night drags on, and I toss till dawn … And now my heart is broken. Depression haunts my days. My weary nights are filled with pain as though something were relentlessly gnawing at my bones" (*Job 7:3-4; 30:16-17 NLT*).

Throughout history, many well-known people reported fibromyalgia-like symptoms, including Florence Nightingale, who became ill while working on the front lines during the Crimean War (1854-1856) and was later bedridden much of the rest of her life with pain and fatigue resembling fibromyalgia.[1]

Originally, this mysterious illness that has been studied since the 1800s was referred to by a variety of names, including hysterical paroxysm, muscular rheumatism and fibrositis. The term "fibromyalgia" was first coined by doctors in 1976 in an

effort to describe its primary symptom (*fibro*, meaning fibrous tissue; *my*, meaning muscle; and *algia*, meaning pain).[1] And, in 1987, fibromyalgia was first recognized by the American Medical Association (AMA) as a "true" illness and the cause of disability.[2] Yet, despite the widespread complaints of fibromyalgia symptoms that have persisted, many individuals and medical professionals continue to believe that this condition is psychiatric or psychosomatic. But, that is changing.

Separating Myth from Fact

Myth: Fibromyalgia is all in a person's head.

Fact: Fibromyalgia is a real, complex illness that is characterized by a variety of symptoms, above all persistent and widespread pain with multiple tender points, poor quality of sleep and fatigue.[3] This condition is included in the *World Health Organization Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems* published in 1992. Unfortunately, fibromyalgia is sometimes thought of as the "garbage-can diagnosis," says Connie Leudtke, RN, nursing supervisor of the Fibromyalgia and Chronic Fatigue Clinic at Mayo Clinic, Rochester, Minn. In essence, if doctors can't find anything else wrong, they say the individual has fibromyalgia.[4]

Because fibromyalgia is defined by a list of symptoms, most doctors believe that individuals' symptoms are real. But, because these symptoms can't be reversed or cured, they often don't believe it's caused by an underlying disease. In addition, since individuals with fibromyalgia don't look sick, it's difficult to convince others that there is anything wrong with them, especially since the symptoms come and go. In fact, people often assume that those complaining of fibromyalgia symptoms are faking their problems to get out of work or to lighten their load at home.[5] But, more people are understanding that fibromyalgia is a real problem, usually because they know someone who has it.[4]

Myth: Fibromyalgia is difficult to diagnose.

Fact: It can take some time to diagnose fibromyalgia, oftentimes because doctors will need to run many tests to rule out other diseases and conditions first. And, there are no blood or X-ray tests to help doctors diagnose fibromyalgia. However, in 1990, the American College of Rheumatology developed a set of criteria that helps doctors diagnose fibromyalgia, and in May 2010, it published new provisional criteria to address certain limitations to the 1990 criteria. Under the 1990 criteria, pain was the only symptom mentioned. To be diagnosed, the patient had to have pain in all four quadrants of the body and in the axial skeleton (bones of the head, throat, chest and spine) that has been present on a more or less continuous basis for at least three months, and pain in at least 11 of 18 tender points, which are specific spots on the body that hurt when pressure is applied. The new 2010 criteria take into account more symptoms, including fatigue, waking unrefreshed, cognitive symptoms and somatic symptoms, such as headache, weakness, bowel problems, nausea, dizziness, numbness/tingling and hair loss. The new criteria also provide a method for monitoring symptom severity, and they provide flexibility: The same person can have different results at different times. The researchers behind this new criteria say they are about 88 percent accurate.[6]

Myth: The mind has nothing to do with fibromyalgia symptoms.

Fact: While fibromyalgia is not all in the mind, the mind does play a role in fibromyalgia symptoms. "Studies have shown that anxiety that occurs in anticipation of pain is much more problematic than the pain experience itself. In that sense, the mind has a negative impact on symptoms," says Dr. Leudtke. "Many of the people who come to our fibromyalgia clinic are perfectionists who have very high expectations for themselves; likewise, they can't adjust to more realistic expectations after they develop fibromyalgia symptoms. These people have difficulty learning to relax. They may push through the pain and keep doing activities to the point they crash and burn and need extra time to recover. So, the pain keeps reinforcing itself in a never-ending cycle."[4]

Fibromyalgia is a real, complex illness that is characterized by a variety of symptoms, above all persistent and widespread pain with multiple tender points, poor quality of sleep and fatigue.

Myth: Fibromyalgia affects only women and older adults.

Fact: Men do suffer from fibromyalgia. However, women are 10 times more likely than men to get fibromyalgia syndrome. And, while fibromyalgia is usually diagnosed between the ages of 20 and 50, it can occur in individuals of all ages, including children.[3]

Myth: There is a magical diet for fibromyalgia.

Fact: There may be anecdotal evidence, but there is no research-based evidence that shows that any particular substance in a diet will cause symptoms, or that removing any substances will make the pain go away. However, people with fibromyalgia

do tend to use more dietary supplements, and some think that they should avoid certain foods, such as refined flour and sugar, sugar substitutes, the caramel color in some soft drinks or carbonated drinks in general.[4]

Myth: There are no medicines to treat fibromyalgia.

Fact: Doctors can recommend and prescribe several medicines to help reduce the pain of fibromyalgia and improve sleep. Common choices include analgesics, antidepressants and anti-seizure drugs.[7]

Analgesics. Acetaminophen (Tylenol and others) can ease the pain and stiffness, but its effectiveness varies. Tramadol (Ultram) is a prescription pain reliver that can be taken with or without acetaminophen. Doctors also may recommend nonsteroidal anti-inflammatory drugs, such as ibuprofen (Advil, Motrin and others) or naproxen sodium (Aleve and others), in conjunction with other medications.

Doctors can recommend and prescribe several medicines to help reduce the pain of fibromyalgia and improve sleep.

Antidepressants. Duloxetine (Cymbalta) and milnacipran (Savella) can help ease pain and fatigue. And amitriptyline or fluoxetine (Prozac) can promote sleep.

Anti-seizure drugs. Epilepsy medications can reduce certain types of pain. For instance, pregabalin (Lyrica) was the first drug approved by the U.S. Food and Drug Administration to treat fibromyalgia, and Gabapentin (Neurontin) is sometimes helpful in reducing fibromyalgia symptoms.

Myth: Exercise and overactivity are not recommended for people with fibromyalgia.

Fact: Many people with fibromyalgia avoid exercise because they fear increased pain. Yet, while it is difficult for individuals with fibromyalgia to exercise because of deep muscle pain, morning stiffness and painful tender points, aerobic exercise can help ease fatigue, minimize pain, improve quality of sleep and improve mood. In fact, numerous studies show that exercise is one of the most important treatments for fibromyalgia. Regular exercise increases the body's production of endorphins, natural painkillers that also boost mood.[8] However, individuals need to pace themselves and set realistic goals for each day. Overdoing it on good days may exacerbate symptoms by doing too much.[5]

Physical therapy also can help relieve fibromyalgia pain and stiffness by relaxing tense muscles. A physical therapist can show individuals the proper way to stretch painful muscles to get optimal relief, and they often use hydrotherapy (moist heat and ice packs) to ease pain more.[8]

Myth: Fibromyalgia can cause lupus.

Fact: While lupus is an autoimmune disease with symptoms similar to fibromyalgia, and they often are confused with one another, they are separate conditions. Lupus is much rarer and can be verified with a blood test. And, while lupus is often a precursor to fibromyalgia (it's estimated that 30 percent of lupus patients develop fibromyalgia), it is almost certain that fibromyalgia is not a direct cause of lupus.[9]

Myth: Fibromyalgia can cause serious damage to the body.

Fact: Fibromyalgia patients have consistently reported an increase in the severity of symptoms such as pain that results in a decreased level of functioning, which in turn leads to decreased muscle deconditioning. However, fibromyalgia is limited to causing insurmountable damage to a patient's lifestyle; it does not cause progressive deterioration to the body.[3]

Dispelling the Myths Now

It is often difficult to believe that a disease is present in fibromyalgia patients, because like many with chronic conditions, they show no telltale outward signs of illness. However, time has proved that fibromyalgia is indeed a real illness. And, while it is incurable, lifestyle changes and a few medications may help to ease patients' pain and return them to normal functioning lives. As more information circulates to educate the population about the myths and facts of fibromyalgia, it is hoped that the history of fibromyalgia — the days when the disease was considered a psychiatric or psychosomatic disorder — will be just that: past history. ❖

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References

1. About.com. History of Fibromyalgia. Accessed at chronicfatigue.about.com/od/fibromyalgia/p/historyfm.htm.
2. Fibromyalgia & Fatigue Centers. How to Discuss with Your Family. Accessed at www.fibroandfatigue.com/how-to-discuss-with-your-family.html.
3. Fibromyalgia Symptoms. Fibromyalgia Syndrome: Common Fibromyalgia Myths and Misconceptions. Accessed at www.fibromyalgia-symptoms.org/myths.html.
4. Mayo Clinic. Fibromyalgia Misconceptions: Interview with a Mayo Clinic Expert. Accessed at www.mayoclinic.com/health/fibromyalgia/AR00056.
5. Fibromyalgia Symptoms. 5 Fibromyalgia Myths. Accessed at www.fibromyalgia-symptoms.org/myths-about-firbromyalgia.html.
6. Dellwo, A. The Fibromyalgia Diagnosis. About.com. Accessed at chronicfatigue.about.com/od/diagnosingfmscfs/a/diagnosingfibro.htm.
7. Mayo Clinic. Fibromyalgia Treatments and Drugs. Accessed at www.mayoclinic.com/health/fibromyalgia/DS00079/DSECTION=treatments-and-drugs.
8. WebMD. Fibromyalgia Treatments. Accessed at www.webmd.com/fibromyalgia/guide/fibromyalgia-treatments.
9. Groshell, H. Most Common Fibromyalgia Myths. Fibromyalgia Free Life. Accessed at fibromyalgiafreelife.com/fibromyalgia-treatment-information/most-common-fibromyalgia-myths/.

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A Collaborative Approach to Leadership

"Effective leadership means finding ways to accomplish goals. I find that the best path is by collaborating with others who share your vision. Leadership is a team sport." —Todd Levine

by TRUDIE MITSCHANG

AN INBRED CURIOSITY and compassionate approach to patient care has served Dr. Todd Levine well throughout his illustrious career. A thought leader when it comes to innovating best practices for patients suffering from neurological disorders, Dr. Levine is a driving force behind the unique practice capabilities of Phoenix Neurological Associates, located in Phoenix, Ariz.

For Dr. Levine, a passion for relationship building is countered only by his enthusiasm for problem-solving.

A Passion for Patients and Problem-Solving

Dr. Levine has long been comfortable wearing numerous hats: He is the founder and director of the Samaritan ALS clinic; co-director of the neurophysiology department at Banner Good Samaritan Medical Center; and a clinical assistant professor at the University of Arizona in neurology. He also conducts extensive research in diseases of the nerve and muscle, he continues to publish his findings in numerous peer-reviewed journals, and he is on the advisory board of *IG Living* magazine. But, he says, he is most proud of his ability to balance the rigorous research demands of an academic career with the accessibility and relaxed bedside manner required of a private-practice physician.

"When I finished my fellowship training, I wanted to focus on neuromuscular diseases while continuing to practice with an academic emphasis," he explains. "The city of Phoenix offered a good environment for that vision because there was no medical school here, and it allowed us to build a presence that really combines the best of both worlds."

Phoenix Neurological Associates employs six board-certified neurologists with a combined experience of more than 90 years in treating all types of neurological problems. Dr. Levine notes that the center also boasts full academic/research capabilities, with a CLIA-certified pathology lab and an infusion center, making it one of the most unique private practice settings in the country.

A father of three, Dr. Levine carefully balances family time with a dedication for getting to know his patients — a commitment that is demonstrated by his involvement in various fundraisers and awareness walks, or simply taking the time during an ALS clinic to share a joke with his patients. For Dr. Levine, a passion for relationship building is countered only by his enthusiasm for problem-solving.

"I think what is exciting for me is discovering new ideas and developing them — my personal bias is that one reason academics tend to be leaders is that they always ask questions and are

looking at patients to see what can be learned from them," he says. "Whether you see a Lou Gehrig's patient and discover what it is that makes their case unique, or you're looking at why some patients respond to IVIG and others to prednisone, it's fascinating to look at the puzzle pieces and figure out the best way to put them all together."

Groundbreaking Work with IVIG

The benefits of intravenous immune globulin (IVIG) for patients with neurological and autoimmune diseases are often described as "miraculous." Dr. Levine's work with IVIG has been groundbreaking to say the least. In a recent presentation, Dr. Levine outlines how a high number of patients with small fiber neuropathies have immune disorders. Previously felt to be untreatable, the patient series examined how treating these patients with IVIG dramatically reduced pain and actually helped nerves begin a regrowth process, potentially offering a whole new treatment option for patients with small fiber neuropathy.

"Up until a few years ago, our typical series of tests for neuropathy did not include a specific objective test for small nerve fibers," he says. "About a decade ago, we found out we could do a skin biopsy and look at small nerves to determine if they were sick or healthy. Unfortunately, most doctors do not think to request the biopsy, which is a shame because patients with this disorder who are treated with IVIG see a dramatic improvement within three to six months, and the positive impact on quality of life is profound."

As he looks to the future, Dr. Levine is excited about one of his newest projects: the formation of a network of physicians involved in the treatment of immune-mediated neurological disorders.

Planning for the Future of Treating Neurological Disorders

As he looks to the future, Dr. Levine is excited about one of his newest projects: the formation of a network of physicians involved in the treatment of immune-mediated neurological disorders. "The Knowledge Infusion Network, or KIN as we're referring to it, will provide a collaborative platform for the experts in our field, allowing us to take advantage of our combined practice experience and knowledge to create standards and protocols around the use of IVIG for a range of disorders," Levine states. "We anticipate KIN becoming an influential clinician-led network that will drive the way patient care is directed and facilitated, specifically in the area of specialty immune-mediated neurological diseases."

With an emphasis on education and collaboration, KIN will help to put physicians back into the center of the decision-making process when it comes to treatment protocols and recommendations. The network will include clinicians from the country's top academic institutions, many of whom are working on groundbreaking studies, as well as those in private practice. What this means for patients and the industry as a whole is that when the network suggests new treatment methods, the recommendations will carry more credence, especially with the insurance companies.

"Leadership is about accomplishing goals, and often the best way to do that is by collaborating with others who share your vision," says Dr. Levine. "When we come together with a common goal, there is an exponential increase in terms of what can be achieved." ❖

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

Regaining Quality of Life

A rare neuromuscular disease left once-active senior Thelma Christison too weak to get out of bed. But intravenous immune globulin (IVIG) has helped her to significantly recover.

by TRUDIE MITSCHANG

Thelma Christison and her husband, Chet, are dealing with her long-awaited diagnosis of immune-mediating necrotizing myopathy, a rare neuromuscular disease that has altered their way of life.

IN JULY 2001, Thelma Christison's sister came for a visit, and during an afternoon of errand running, their car came to a stop in the middle of a busy intersection. Her children remember laughing later about their mom's stamina; even though she was nearly 70 at the time, she hopped out of that car and helped push it to the side of the road. Just four months later, Thelma would be too weak and incapacitated to lift the newest of her 10 grandchildren. The Fresno, Calif., resident didn't know it at the time, but she was suffering from the early stages of a rare neuromuscular disease that would alter the course of her life.

"I had always been very healthy, and at first I thought the symptoms were all in my head," says Thelma. "My first doctor was puzzled too — early blood tests showed I had high CK levels and I was taken off all my medications to see if Lipitor or another prescription was the problem. But instead of getting better, I got worse."

Doctors were puzzled about why Thelma's creatine kinase (CK) levels were high. CK is an enzyme that becomes elevated in the bloodstream by conditions that damage the skeletal muscles, and also can be influenced by cholesterol lowering medications, which is what Thelma's first doctors suspected.

Thelma's journey to diagnosis was difficult given her weak physical state. She was frequently bedridden and her daughter, Terri, who is a chemist, acted as a patient advocate, going with her to all her doctor's appointments and often helping to interpret the sometimes complex assessments of her mother's health crisis.

After struggling for several months to find an answer to her deteriorating condition, Thelma began taking prednisone and improved dramatically. But whenever the prednisone dose was reduced, her symptoms returned. Thelma switched doctors, a move that led her to be referred to neurologist Dr. Jonathan Katz. Dr. Katz assessed her symptoms and her muscle biopsy, which led to the diagnosis of an immune-mediated necrotizing myopathy that was suspected to be related to her statin medication.

Understanding Immune-Mediated Necrotizing Myopathy Associated with Statins

Immune-mediated necrotizing myopathy is a newly reported muscle disease that responds to immune medications. It is less known than polymyositis, which is easier to diagnose because of the chronic muscle inflammation seen on biopsy. All these disorders affect skeletal muscles (those involved with making movement) on both sides of the body. Here are some facts about this new condition:

- The disease presents with progressive muscle weakness that starts in the proximal muscles (muscles closest to the trunk of the body), which eventually leads to difficulties climbing stairs, rising from a seated position, lifting objects or reaching overhead.
- It results in elevated CK levels in the thousands.
- It usually begins while taking statins, and continues despite discontinuation.
- Muscle biopsies show no evidence of inflammatory cells and, instead, show only necrosis (dying tissue).
- The disease is responsive to immune

At 80 years old, Thelma is thankful that her IVIG treatments have restored much of her health and she is able to enjoy her five children and 10 grandchildren.

medications like IVIG, prednisone and others.

• Thelma was one of the first patients diagnosed with this new disorder and was one of 25 cases reported in one of the first descriptions of the disease, which was reported on in the February 2010 issue of *Muscle & Nerve*.

Thelma was re-treated with 60 mg per day of prednisone, and she gradually improved. But the doses could never be lowered enough to avoid the side effects, and relapses kept occurring whenever tapering was attempted. After prednisone was stopped, she improved with cyclosporine, but it also had to be stopped because of kidney failure. Several other agents were attempted but did not work well, and she had numerous relapses of weakness. Thelma also underwent a second muscle biopsy that, according to Dr. Katz, confirmed she was suffering from necrotizing myopathy. Dr. Katz finally decided to start her on a regimen of IVIG, a move that would dramatically improve Thelma's physical strength and energy levels.

Like many patients who are prescribed IVIG off label, Thelma undergoes an annual ritual of being denied coverage for her infusions.

An Uphill Battle with Insurance

Like many patients who are prescribed IVIG off label, Thelma undergoes an annual ritual of being denied coverage for her infusions. Thankfully, Dr. Katz and his office team have acted as advocates on her behalf, getting her approved annually for another year of treatment. "They turn me down every year, and then Dr. Katz has to go back and prove to them that it is necessary," Thelma says.

Even though Thelma has obviously responded positively to her infusions, which have tapered off to once every six weeks, her insurance battle is not an unusual one. Most often, when an insurance company denies coverage of IVIG, it is on the grounds that the treatment is considered experimental or investigational. Insurers may take this position when IVIG — indeed, any treatment — is prescribed for what is called an "off-label use." An off-label use is one that is not listed in the labeling approved by the U.S. Food and Drug Administration. As a general rule, when an insurer denies coverage of an off-label use, it is very hard to convince them to make an exception — making Thelma's case even more unique. Her case has been so fascinating that Dr. Katz and several other physicians used her as an index case in a medical journal article about new IVIG-responsive muscle diseases. The article was published in October 2009.

"Dealing with this insurance company was as frustrating as you can ever imagine," says Dr. Katz. "The condition was clearly responsive to immune medications, and we had tried just about everything else before starting the IVIG. We made every effort, including publishing with doctors from Harvard in a respected peer-reviewed journal. We provided the insurance company with all the information they could ever want about the medications, improvements and relapses. Nonetheless, they would send us these thoughtless notes saying the therapy was 'experimental,' whatever that means. They asked us for the same records over and over, and did nothing to facilitate finding someone who could just listen to us. We'd kick and scream, but Thelma still missed some of her therapy, and my office personnel put in hours of unnecessary work."

From a Dire to a Positive Prognosis

Thelma has been undergoing IVIG treatments for more than three years now, and she remains in complete remission. She receives her treatments in a homecare setting, and each infusion takes about four hours to complete, a time investment Thelma says is well worth the effort. "I have five children and 10 grandchildren, so I have a lot of motivation to get well," she says while laughing. "When I was first diagnosed, I would have the grandbabies come sit beside me on the couch. I was afraid to pick up the little ones because I was so weak — I thought I would drop them."

At 80 years old, Thelma knows she will never be as active as she once was, but she is thankful that a "miraculous" treatment like IVIG exists and that it has restored so much of her quality of life. "I went from being bedridden to being able to go on trips and cruises since I started IVIG," she says. "I've gotten strong enough to walk, make meals, and lead a somewhat normal life." ❖

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

Under the Skin Is In

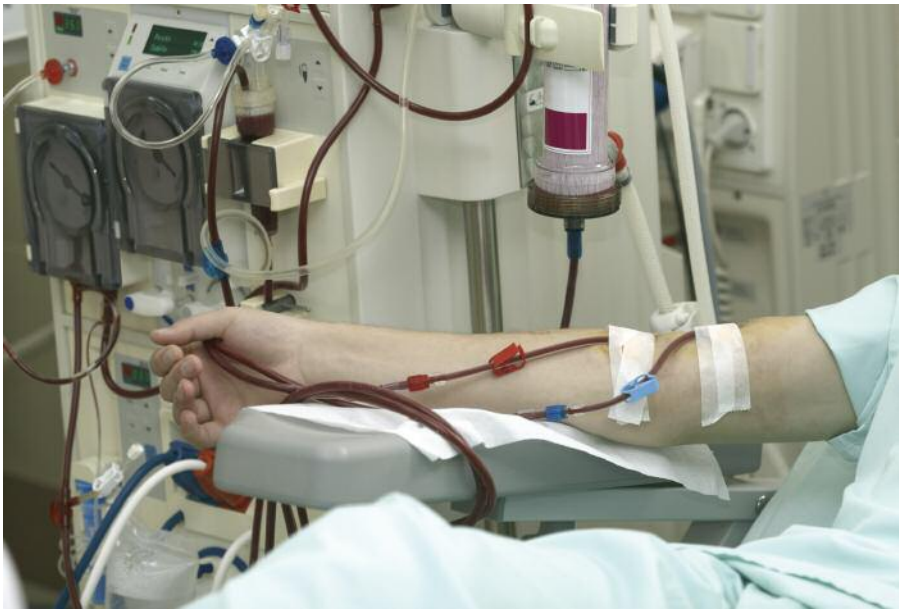
Subcutaneous immunoglobulins for primary immunodeficiency have arrived.

by KEITH BERMAN, MPH, MBA

IT WAS 1979, and the 24-year-old woman with a long history of severe and life-threatening infections — including episodes of sinusitis, otitis media, sepsis and pneumonia — was again in serious trouble. Unable to tolerate the pain of injections of large volumes of intramuscular immunoglobulin (IMIG) needed to raise her serum IgG to a protective range, her serum immunoglobulin (Ig) levels were undetectable when she was admitted to the hospital with cellulitis and fever.

With intravenous immunoglobulin (IVIG) not yet available, Dr. Melvin Berger and colleagues at the National Institutes of Health (NIH) promptly administered a loading dose of IMIG, and followed with more IM injections that brought her serum IgG level up to only 270 mg/dL, well below protective levels.[1] Meanwhile, a chronic pulmonary infection and culture-positive sinusitis would not clear up. The NIH team decided to resort to a different approach: The young woman was trained to self-administer small, slow subcutaneous infusions of standard 16% IMIG on a daily basis.

While IgG clumps and fragments in IMIG cause severe anaphylactic reactions when given by the IV route, the patient tolerated the product quite well. Her sinopulmonary and sepsis problems disappeared. She continued her daily subcutaneous infusions right through a normal full-term pregnancy shortly thereafter, boosting her dose along the way to maintain a protective IgG level. Other patients were started on subcutaneous therapy with IMIG.



But a few years later, intravenous immunoglobulin (IVIG) became available, and with it the ability to dose large quantities of IgG antibody in a single infusion every three to four weeks. Suddenly, the subcutaneous route for Ig infusions in patients with primary immunodeficiency disorders (PIDDs) all but disappeared in the United States.

You Can't Keep a Good Delivery Option Down

While these preparations of largely intact IgG monomers and dimers were heralded for being the first to allow administration of very large doses, physicians and infusion nurses quickly learned that IVIG products are not without their own tolerability issues. Despite mitigation strategies that include pre-hydration, pre-medication, slowing the infusion rate and switching product brands, some patients may still experience non-serious but unpleasant adverse effects such as headache and nausea. Very infrequently, more severe reactions can occur, including anaphylaxis and aseptic meningitis. An entirely separate challenge may be posed by immunodeficient children in particular who have poor IV access.

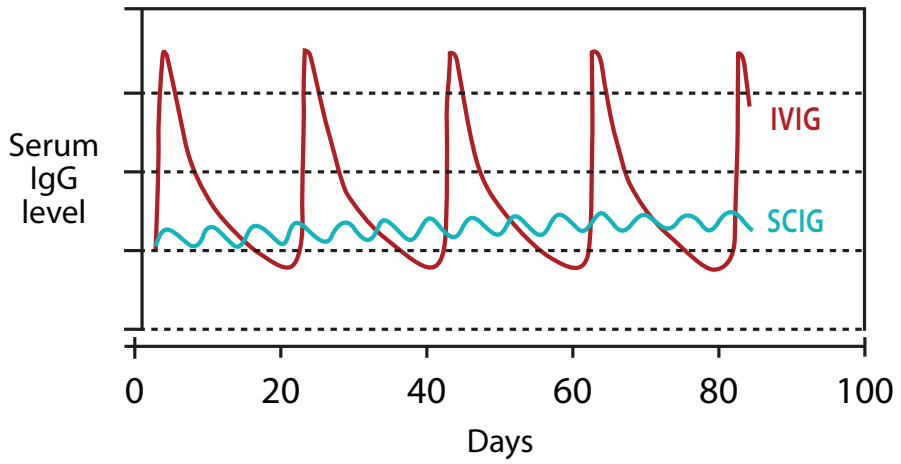
Taking note of the long experience of Scandinavian physicians treating PIDD patients with subcutaneous Ig,[2,3] in 1998, Dr. E. Richard Stiehm and colleagues at the University of California

Los Angeles reported successful use of the subcutaneous route for administration of IVIG in eight patients with venous access problems, a history of IVIG-related anaphylaxis or rapid IVIG catabolism.[4]

Finally in 2006, CSL Behring introduced Vivaglobin, a 16% subcutaneous immunoglobulin (SCIG), providing physicians with their first FDA-approved option after years of prescribing off-label subcutaneous use of licensed IVIG products. Vivaglobin has now been replaced by Hizentra, an even more concentrated 20% product approved in March 2010. Further expanding the choices, the FDA has recently approved subcutaneous administration of three licensed 10% IVIG products: Grifols' Gamunex-C, Baxter's Gammagard Liquid and Kedrion's Gammaked.

Today, patients are trained to perform their subcutaneous infusions using convenient mechanical and battery-powered syringe pumps and administration sets that allow product delivery to one, two, three, four or more adequately spaced sites (typically the abdomen, lateral hip, thigh and/or upper arm). Infusions are performed on a weekly basis (or sometimes more often), and typically can be completed in an hour or less. Local redness and swelling at the infusion site is common, but in most patients, it dissipates within a few hours and tends to diminish with more procedures over time. Very importantly, the frequency of severe systemic adverse reactions, and specifically in patients who experienced these reactions with IVIG, is extremely low. This is immediately attributable to a much lower peak serum IgG level than IVIG administered directly into the circulation.

Figure 1. IVIG vs. SCIG: Typical fluctuation patterns in serum IgG levels over time



For those who can comfortably manage the SCIG home self-infusion procedure, there are clear quality-of-life-related advantages over scheduled visits for IVIG infusions.

Other Benefits of Subcutaneous Delivery

Self-administering Ig at home is not for everyone with PIDD. Careful selection of patients who are both capable and motivated is critical. But for those who can comfortably manage the SCIG home self-infusion procedure, there are clear quality-of-life-related advantages over scheduled visits for IVIG infusions:[5]

- ***No missed school/work days.*** The patient does not need to miss school or work to receive infusions at a clinic typically open only during normal business hours.
- ***Scheduling flexibility.*** SCIG infusions can be completed whenever the patient desires, except when engaged in sports or exercise activity.
- ***No venous access issues.*** For patients with difficult IV access, there is no need for surgical implantation or maintenance of venous access devices.
- ***Patient autonomy.*** Self-infusion promotes a positive sense of personal control over the patient's lifelong immunodeficiency disorder.

Further, because subcutaneous IgG distributes gradually from the infusion site(s), patients experience far less fluctuation in serum IgG levels than with IVIG infusions every three to four weeks (see Figure 1). For similar doses, the trough IgG level for a patient on SCIG therapy is usually marginally higher than the trough level on IVIG, but the overall quantity of circulating IgG over time — the so-called "area under the curve" — favors IVIG. At present, there is no substantive evidence that either delivery route yields a lower serious bacterial infection risk.

In Development: Much More, Much Less Often

For many PIDD patients who tolerate IVIG infusions well, the potential advantages of SCIG — including time flexibility and freedom from a clinic IV infusion session — are outweighed by the need to set up and self-infuse SCIG at least every week. But soon, this barrier could be eliminated if a new "facilitated" SCIG currently being co-developed by Baxter Healthcare and Halozyme Therapeutics proves safe and effective.

Dubbed "HyQ," this investigational product involves two sequential phases. First, recombinant hyaluronidase is infused subcutaneously. This synthetic version of a naturally-occurring human enzyme increases connective tissue permeability by digesting hyaluronic acid, a carbohydrate polymer present throughout the extracellular space that acts to "cement" cells together. This facilitates dispersion and absorption of the 10% IgG protein solution that follows.

The objective of this novel approach is to enable patients to self-administer a single large dose of SCIG every three or four weeks, using only one or two infusion sites. Preliminary results of a Phase III study of "HyQ" in 89 patients with PIDD appear encouraging; the acute serious bacterial infection rate was just 0.025 per patient per year, far below the required threshold for regulatory approval. Baxter submitted a Biologics License Application for "HyQ" earlier this year.

Licensed Subcutaneous Immunoglobulin Products

	Hizentra	Gamunex-C	Gammagard Liquid	Gammaked
Manufacturer	CSL Behring	Grifols	Baxter Healthcare	Kedrion Biopharma
IgG Concentration	20%	10%	10%	10%

More Diagnoses Under the SCIG Tent?

Interest in the advantages of SCIG has prompted a number of investigators here and abroad to evaluate this alternative to IVIG in certain other disorders where Ig therapy is needed on a protracted basis. Recent small studies and case reports suggest that SCIG therapy may be safe and therapeutically equivalent to IVIG infusions in properly selected patients with chronic inflammatory demyelinating polyneuropathy (CIDP),[6] multifocal motor neuropathy (MMN)[7,8] and polymyositis and dermatomyositis.[9]

SCIG Past and Future

Back in 1952, Dr. Ogden Bruton, a pediatrician at Walter Reed Army Hospital, described the first case of PIDD: an 8-year-old boy with profoundly depressed serum immunoglobulin levels later shown to be X-linked agammaglobulinemia. Dr. Bruton treated that first case of PIDD with subcutaneous doses of immunoglobulin.

Over the decades that followed, physicians returned to subcutaneous delivery to provide protective Ig replacement therapy for patients who could not tolerate painful IMIG injections, or who had specific contraindications to IVIG therapy. Today, thousands of patients with PIDD self-manage their condition using one of the four licensed, well-proven SCIG product options.

There's no question about it: Ig delivery under the skin is in, and all indications suggest it will become the choice of increasing numbers of patients who require chronic Ig replacement therapy. ❖

Preliminary results of a Phase III study of "HyQ" in 89 patients with PIDD appear encouraging.

References

1. Berger, M, Cupps, TR, and Fauci, AS. High-Dose Immunoglobulin Replacement Therapy by Slow Subcutaneous Infusion During Pregnancy. *Journal of the American Medical Association*, 1982 May 28; 247(20):2824-5.
2. Gardulf, A, Hammarstrom, L, Smith, CIE. Home Treatment of Hypogammaglobulinemia with Subcutaneous Gammaglobulin by Rapid Infusion. *Lancet*, 1991; 338:162-66.
3. Abrahamsen, TG, Andersen, H, and Bustnes, A. Home Therapy with Subcutaneous Immunoglobulin Infusions in Children with Congenital Immunodeficiencies. *Pediatrics*, 1996; 98:1127-31.
4. Stiehm, ER, Casillas, AM, Finkelstein, JZ, et al. Slow Subcutaneous Human Intravenous Immunoglobulin in the Treatment of Antibody Immunodeficiency: Use of an Old Method with a New Product. *Journal of Allergy and Clinical Immunology* 1998; 101:848-9.
5. Berger, M. Subcutaneous Immunoglobulin Replacement in Primary Immunodeficiencies. *Clinical Immunology*, 2004; 112:1-7.
6. Lee, DH, Linker, RA, Paulus, W, et al. Subcutaneous Immunoglobulin Infusion: A New Therapeutic Option in Chronic Inflammatory Demyelinating Polyneuropathy. *Muscle and Nerve*, 2008 Mar; 37(3):406-9.
7. Harbo, T, Andertsen, H, Hess, A, et al. Subcutaneous Versus Intravenous Immunoglobulin in Multifocal Motor Neuropathy: A Randomized, Single-Blinded Cross-Over Trial. *European Journal of Neurology*, 2009 May; 16:631-8.
8. Harbo, J, Andersen, H, and Jakobsen, J. Long-Term Therapy with High Doses of Subcutaneous Immunoglobulin in Multifocal Motor Neuropathy. *Neurology*, 2010 Oct 12; 75(15):1377-80.
9. Schleinitz, N, Jean, E, Benarous, L, et al. Subcutaneous Immunoglobulin Administration: An Alternative to Intravenous Infusion as Adjuvant Treatment for Dermatomyositis? *Clinical Rheumatology*, 2008; 27(8):1067-8.

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IVIG May Confer Relief in Specific Types of Neuropathy Associated with Sjögren's Syndrome

Administration of high-dose intravenous immunoglobulin (IVIG) may provide symptomatic relief in patients with sensorimotor neuropathy or nonataxic sensory neuropathy associated with primary Sjögren's syndrome, according to a retrospective analysis of 19 French Sjögren's patients. The median duration of neuropathy in these patients was nine years at the time of treatment. All patients received 2 g/kg of IVIG per month in divided doses for a median of seven months. Response was assessed using the Modified Rankin Scale and a global evaluation by the practitioner.

All five patients with sensorimotor neuropathy, all four patients with nonataxic neuropathy and a sole patient with conduction block improved or stabilized on IVIG therapy. In contrast, just two of nine patients with ataxic neuropathy improved, while three remained stable and four worsened. After four to 12 months of treatment, five treatment-responsive patients were able to have their IVIG infusions spaced to every two to three months. Ten of 13 steroid-dependent patients were able to reduce their prednisone dosage from an average of 15 mg daily before IVIG to 10 mg daily with IVIG therapy.

"Symptomatic treatment should be tested in patients with Sjögren's syndrome without necrotizing vasculitis-related neuropathy," the investigators concluded. "Further studies are necessary to investigate the optimal number of IVIG courses necessary to definitively assess the efficacy or the failure of the treatment."

Rist, S, Sellam, J, Hachulla, E, et al. Experience of intravenous immunoglobulin therapy in neuropathy associated with primary Sjögren's syndrome: A national multicentric retrospective study. Arthritis Care & Research, *2011 May 16 [Epub ahead of print].*

Two Full Doses of Influenza Vaccine Improves Immunogenicity Versus Two Half-Doses in Infants

To assess whether two full doses of trivalent inactivated influenza vaccine (TIV) could improve immunogenicity versus two half-doses without increasing reactogenicity in infants (aged 6 to 11 months) and toddlers (aged 12 to 23 months), Canadian researchers randomized previously unimmunized children to receive one or the other regimen of 2008-2009 split TIV. Sera were collected from 252 participants at enrollment and at 27 and 45 days after the second injection. The primary immunogenicity outcome was superiority of the full-dose versus the half-dose, defined as a greater than 10 percent increase in the seroprotection rate.

In toddlers, post-immunization seroprotection rates exceeded 85 percent for all three flu vaccine components using both doses. In infants, however, the full dose induced higher responses for all three vaccine components. Rates of fever were not increased among full-dose versus half-dose recipients in either age group.

Investigators at the British Columbia Centre for Disease Control concluded that administration of two full TIV doses may improve immunogenicity without increasing reactogenicity in infants, and suggested that current TIV dosing recommendations for young children warrant additional evaluation.

Skowronski, DM, Hottes, TS, Chong, M, et al. Randomized controlled trial of dose response to influenza vaccine in children aged 6 to 23 months. Pediatrics, *2011 Aug;128(2):e276-89.*

Secondary Prophylaxis with Factor VIII/VWF Concentrate Sharply Reduces Bleeding in Patients with von Willebrand Disease

Long-term prophylactic administration of Octapharma's Wilate factor VIII/von Willebrand factor (VWF) concentrate dramatically reduced bleeding episodes in 24 patients with von Willebrand disease (VWD) who were referred with a bleeding score >2 prior to diagnosis and recurrent bleeds associated with anemia despite use of on-demand VWF therapy, German hematologists reported at the International Society on Thrombosis and Hemostasis.

Based on individual 24-hour post-infusion VWF:RCo recoveries, a median dose of 40 IU/kg of Wilate (range 20 to 47 IU/kg) was given on a twice weekly (15 patients), three times weekly (seven patients) or four times weekly (two patients) basis. The median duration of prophylaxis was three years. Within a 12-month period, hemoglobin levels returned to normal values in all patients. Recurrent bleeding episodes stopped in 23 of 24 patients. Over a 12-month observation period, the monthly bleeding frequency (3 vs. 0.07; $p<0.001$) and bleeding score (3 vs. 0, $p<0.001$) were significantly reduced compared with the pre-prophylaxis/ pre-diagnostic values.

The authors concluded that the use of secondary prophylactic VWF replacement therapy with Wilate is a well-tolerated, highly beneficial treatment modality for patients with VWD who present with recurrent bleeding activity despite on-demand therapy.

Halimeh, S, Kruempel, A, Rott, H, et al. Long-term secondary prophylaxis factor replacement therapy with Wilate in children, adolescents and young adults with von Willebrand disease. XXII Congress of the International Society on Thrombosis and Haemostasis (Kyoto, Japan), July 27, 2011. Oral abstract P-WE-462.

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BioResources

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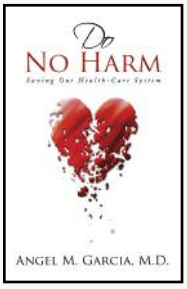

Do No Harm: Saving Our Health-Care System
Author: Angel M. Garcia, MD
Do No Harm outlines the problems that physicians and patients encounter, such as conflicts of interest, problems in reimbursement and primary care shortages. Included are insight and expert advice to patients, physicians and lawmakers on changes that will enhance patient care, the patient-doctor relationship, and offer a reduction in costs.
www.donoharmdrs.com

Autoimmune Diseases-Pipelines for Crohn's Disease, Multiple Sclerosis and Rheumatoid Arthritis
Author: Reportstack
This report focuses on current and pipeline candidate therapeutics and their respective targets for three autoimmune diseases. It reports on the development pipelines for each disease, providing information on company and licensee involvement; active Phase II and Phase III clinical trials and study completion dates; targets involved across the spectrum of launched and preclinical activities; competition among companies developing therapeutics targeting the same or related physiology; pace of development activities across these three diseases; and small or specialty companies with innovative therapy development programs.
www.reportstack.com/product/22552/autoimmune-diseases-pipelines-for-crohns-disease-multiple-sclerosis-and-rheumatoid-arthritis.html

Socialized Healthcare Reform
Author: R. Garth Kirkwood, MD
Socialized Healthcare Reform discusses the numerous problems with the American healthcare system and what must occur before reform can take place. Dr. Kirkwood explains that the nexus between major healthcare businesses (insurance carriers, hospitals and politics) creates conflicted functioning with individual doctor-patient relationships, which furthers the agenda of controlling healthcare spending at the expense of non-conflicted clinical decision-making, while leaving business profits and political goals unscathed. According to Dr. Kirkwood, the business of medicine is privatized and the medicine of medicine is socialized — a skewed reality that cannot be changed unless "the doctor-patient relationship becomes free of external control from any payer and returns to its primary position as the essence of medicine, to be supported and served by the entire system."
www.equalhealthcare.org

Tables of Biologic Therapies (aka WEBbook of Biologic Therapies)
Author: Clinical Immunology Society
This public service targeted to the medical community is a new endeavor intended to offer an authoritative compendium of information on biologic therapies. The tables list biologic therapies currently commercially available and include generic and brand names, therapeutic target, licensed indication and manufacturer. A navigation sidebar on the left lists all current categories.
biologics.clinimmsoc.org

White Book on Allergy
Author: World Allergy Organization
The *White Book on Allergy* is an important initiative by the WAO calling on international and national healthcare policymakers to address early identification of symptoms, early diagnosis and appropriate strategies to manage and control allergies to avoid worsening of severe allergic disease to people at risk and to improve practice in this clinical field of medicine for the benefit of those suffering from the consequences of allergies.
www.worldallergy.org/UserFiles/file/WAO-White-Book-on-Allergy_FINAL.pdf

Drug Promotion and Social Media: Strategies for Best Practices for Pharma Companies
Author: U.S. Food and Drug Administration
This concise FDAnews management report provides a roadmap for avoiding FDA DDMAC (Division of Drug Marketing, Advertising and Communications) enforcement actions as companies transition product promotion and disease awareness campaigns to new social media platforms such as Twitter, Facebook and YouTube. Included are the latest best practices drawn from real-world experiences of companies like AstraZeneca and products like Gardasil and LapBand. Also included are answers to frequently asked questions and insights into what can trigger warning letters or criticism from the FDA.
www.fdanews.com/store/product/detail?display=0&productId=34785&hittrk=11802&utm_source=MagnetMail&utm_medium=email&utm_term=rrhodes@igliving.com&utm_content=BDPSM - 11802 - 8/2/11 - DR/MB/RDD/RDR&utm_campaign=Drug Promotion via Social Media%3A A Roadmap

BioDashboard

CALCULATOR

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective October 1, 2011 through December 31, 2011.

Product	Manufacturer	HCPCS	Hospital Outpatient ASP+5% (per gram)	Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$61.502	$62.088
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$70.308*	$70.308
GAMMAGARD LIQUID	Baxter BioScience	J1569	$74.867	$75.580
GAMMAGARD S/D	Baxter BioScience	J1566	$61.502	$62.088
GAMMAKED	Kedrion	J1599	$74.968*	$74.968
GAMMAPLEX	Bio Products Laboratory	J1599	$74.586*	$74.586
GAMUNEX-C	Grifols	J1561	$74.261	$74.968
PRIVIGEN	CSL Behring	J1459	$69.498	$70.160

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

Calculate your reimbursement online at www.FFFenterprises.com.

REFERENCE TABLES

IVIG/SCIG Reference Table

Product	Indications	Size	Manufacturer
CARIMUNE NF Lyophilized	IVIG: PIDD, ITP	3 g, 6 g, 12 g	CSL Behring
FLEBOGAMMA 5% & 10% DIF Liquid	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
GAMMAGARD LIQUID 10%	IVIG/SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g	Baxter BioScience
GAMMAGARD S/D Lyophilized, 5% or 10%	IVIG: PIDD, ITP, CLL, KD	2.5 g, 5 g, 10 g	Baxter BioScience
GAMMAKED Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Kedrion
GAMMAPLEX Liquid, 5%	IVIG: PIDD	5 g, 10 g	Bio Products Laboratory
GAMUNEX-C Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
HIZENTRA Liquid, 20%	SCIG: PIDD	5 mL, 10 mL, 20 mL	CSL Behring
PRIVIGEN Liquid, 10%	IVIG: PIDD, ITP	5 g, 10 g, 20 g	CSL Behring

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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