

January 2013

BioSupply *Trends*

Special Focus: PLASMA

Q u a r t e r l y

The PIDD Puzzle

Solving the Diagnosis Dilemma

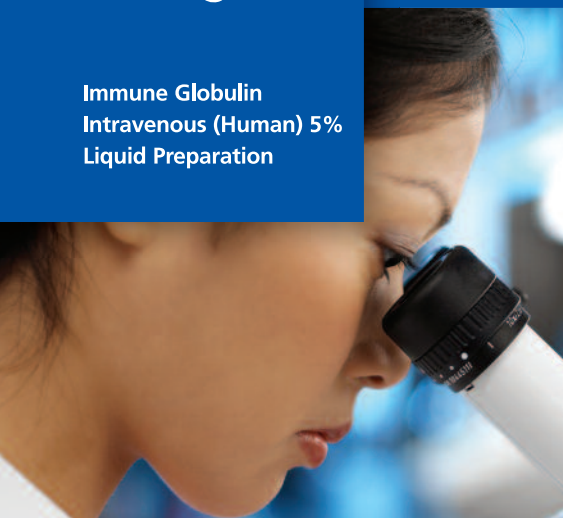
**Plasma Products:
Planning for the Future**

**A Guide to Immune Globulin
Billing and Reimbursement**

In the January 2012 issue of this publication, we ran an advertisement for octagam® [Immune Globulin Intravenous (Human) 5%] that omitted required risk information. The advertisement for octagam® below contains all required risk information.

octagam®

Immune Globulin
Intravenous (Human) 5%
Liquid Preparation



RESEARCHED



REFINED



REASSURED

**Proven clinical efficacy
in patients with
primary humoral
immunodeficiency (PI)^{1,2}**

For more information, please contact us:

Octapharma USA, Inc.

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Fax: 800-554-6744

To report suspected adverse reactions,
contact Octapharma USA, Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch

**Enhanced fractionation
process for
thromboembolic safety³**

**Established
pathogen safety
profile**

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

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

CONTRAINDICATIONS

octagam® 5% liquid is contraindicated in patients who have acute severe hypersensitivity reactions to human immunoglobulin. octagam® 5% liquid contains trace amounts of IgA (not more than 0.2 mg/ml in a 5% solution). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity. octagam® 5% liquid is contraindicated in patients with acute hypersensitivity reaction to corn. octagam® 5% liquid contains maltose, a disaccharide sugar which is derived from corn. Patients known to have corn allergies should avoid using octagam® 5% liquid.

WARNINGS AND PRECAUTIONS

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

References

1. Octagam®, Immune Globulin Intravenous (Human) 5% Liquid Preparation, complete Prescribing Information. 2009.
2. Ochs HD, Pinciaro PJ. Octagam® 5%, an intravenous IgG product, is efficacious and well tolerated in subjects with primary immunodeficiency diseases. J Clin Immunol 2004;24:309-14.
3. Roemisch J, et al. Identification of activated FXI as the major biochemical root cause in IVIG batches associated with thromboembolic events. analytical and experimental approaches resulting in corrective and preventive measures implemented into the Octagam® manufacturing process. WebmedCentral Immunother 2011;2:WMC002002.

Please see Highlights of Prescribing Information on adjacent page.

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Date of Preparation 8/12. GAM5-006-PAD

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For the safe and optimal use of human proteins

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Octagam, Immune Globulin Intravenous (Human), safely and effectively. See full prescribing information for Octagam.

Octagam® [Immune Globulin Intravenous (Human)] 5% Liquid Preparation Initial US Approval: 2004

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

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

RECENT MAJOR CHANGES

Warnings and Precautions – Hyperproteinemia 8/2008

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Intravenous use only.

Indication	Dose	Initial Infusion rate	Maintenance infusion rate (if tolerated)
PI	300-600mg/kg	0.5mg/kg/min	3.33mg/kg/min Every 3-4 weeks

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Octagam 5% liquid if renal function deteriorates.
- For patients at risk of renal dysfunction or thrombotic events, administer Octagam 5% liquid at the minimum infusion rate practicable.

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.
- Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Falsely elevated blood glucose readings may occur during and after the infusion of Octagam 5% liquid with some glucometer and test strip systems.

- Hyperproteinemia, increased serum viscosity and hyponatremia occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome has been reported with Octagam 5% liquid and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infection agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease agent.

ADVERSE REACTIONS

The most serious adverse reactions observed with Octagam® 5% liquid treatment have been immediate anaphylactic reactions, aseptic meningitis, and hemolytic anemia.

Most common adverse reactions with an incidence of >5% during a clinical trial were headache and nausea. **To report SUSPECTED ADVERSE REACTIONS, contact Octapharma at 1-866-766-4860 or FDA at 1-800-FDA-1008 or www.fda.gov/medwatch.**

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

HOW SUPPLIED

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

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About BioSupply Trends Quarterly

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BioSupply Trends Quarterly has a circulation of 40,000, with an approximate readership of more than 100,000 decision-makers who are comprised of general practice physicians, hospital and clinic chiefs of staff and buyers, pharmacy managers and buyers, specialist physicians and other healthcare professionals.

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Plasma Therapies: From Supply to Dosing and Reimbursement



IN COMING YEARS, the number of chronic illnesses treated with lifesaving therapies manufactured from human plasma is predicted to grow. This means more patients, physicians and pharmacists will be impacted by the issues surrounding supply and demand, appropriate and adequate dosing, and billing and reimbursement of these therapies, most notably immune globulin (IG) and albumin. In this plasma-themed issue of *BioSupply Trends Quarterly*, we take a critical look at each of these segments of the plasma market.

In the past, shortages of IG and albumin left physicians and pharmacists hunting for these scarce drugs and often paying exorbitant gray market prices to get them. But, as our article *The Plasma Industry: Investing Today to Ensure IG and Albumin Supply for Tomorrow* explains, the industry is committed to averting future shortages. Manufacturers are addressing the challenge by building additional plasma collection centers and processing capacity to keep ahead of the growing U.S. and worldwide demand for both key products. The article illustrates the big-picture story with charted data that provide a diagram of historical plasma sourcing, plasma fractionation, and intravenous IG (IVIG) and subcutaneous IG (SCIG) and albumin demand.

Patients with genetic and phenotypic primary immunodeficiency disorders (PIDDs) depend on IG to maintain their health and improve their quality of life. In our article *When It Turns Out to Be PIDD: Benefits of Early Diagnosis*, we look at how the rare nature of these disorders tends to delay diagnosis and create roadblocks to treatment. By examining the history of PIDDs, the circumstances in which IVIG or SCIG replacement therapy is indicated, and the appropriate dosing strategies that result both from manufacturer-suggested guidelines and, most importantly, from professional judgment by treating physicians, we can help improve patient outcomes

and facilitate access to these life-sustaining proteins.

Behind the clinical picture of PIDDs are the patients and their families, as well as the physicians who treat them. In our story *XLA: A Patient's Perspective*, we look at the lives of one family that must deal with the daily challenges, heartbreak and loss that come with four children who have X-linked agammaglobulinemia, one of whom succumbed to the disease as an infant. And, in our question-and-answer interview *XLA: A Physician's Perspective*, Dr. Hans Ochs, an authority on PIDDs with a special interest in genes linked to XLA, shares how, thanks to the advent of IG, children who are diagnosed and treated early can go on to lead normal and active lives.

Of course, as anyone who has ever been on the prescribing or receiving end of IG knows all too well, maintaining continuity of care is often difficult due to a cumbersome and complex reimbursement model. The fact is, getting reimbursed, especially for IG, can be a challenge, even for the most experienced providers. In our article *Immune Globulin: A Guide to Billing and Reimbursement*, we give physicians and providers a step-by-step guide to getting authorization, submitting a claim and, if necessary, filing an appeal — all essential to avoiding delays, denials and financial hardship.

As always, we hope you find this issue of *BioSupply Trends Quarterly* educational, insightful and innovative. Looking to the future, we hope to continue to bring you the information and resources that are helpful to you in your practice.

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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

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Office of Mobile Health to Speed Up Medical App Approval



The U.S. House of Representatives has introduced a bill that intends to clarify and shorten the U.S. Food and Drug Administration's (FDA's) assessment process of mobile health apps. The Healthcare Innovation and Marketplace Technologies Act (HIMTA) would form a unique Office of Mobile Health at the FDA to give suggestions on mobile health app issues. The act also would

create a mobile health app developer support program at the U.S. Department of Health and Human Services to help ensure that app developers are operating within privacy regulations.

In 2011, the FDA began regulating a small number of medical apps and released a first draft of guidelines that require mobile health app developers making medical claims apply for FDA approval. But because the FDA is taking between six and 20 months to approve other medical devices, medical app developers are concerned that the approval process for their apps will be delayed.

By 2015, 500 million smartphone users are expected to employ mobile medical apps to do everything from track illness and weight to logging a healthier diet and exercise routine. With the HIMTA bill, it is hoped that the new Office of Mobile Health will be able to keep up with an ever-growing sector of mobile health. ❖

New Bill Will Modify Medical Loss Ratios



The U.S. House of Representatives Energy and Commerce Committee has approved H.R. 1206, the Access to Professional Health Insurance Advisors Act, with a 26-14 vote. The bill will modify the Public Health Service Act to exclude remuneration paid for licensed independent insurance producers, who

provide professional insurance and guidance to the poor, the elderly and small-business owners who do not wholly understand their health insurance options, from administrative cost calculations for purposes of calculating the medical-loss ratio (MLR) of a health insurance plan.

The provision on MLR requires the secretary of Health and Human Services, when a state requests an adjustment of a medical-loss ratio, to defer to the state's findings and determinations as to whether enforcing the required medical-loss ratio may destabilize the individual or small group markets for health insurance. ❖

6M Uninsured Americans to be Hit with Tax Penalty



Beginning in 2014, nearly six million U.S. citizens are expected to purchase health insurance or face an average tax penalty of \$1,200, following a Supreme Court 5-4 decision this past summer that upheld the constitutionality of the Affordable Care Act. In 2010, the non-partisan Congressional Budget Office projected that four million people would be affected by the tax in 2016 when the penalty goes into full effect. However, due to changes in introductory forecasts about the economy, integrating the effects of new federal legislation, as well as lower wages and higher unemployment, the new estimate is closer to six million Americans. The tax will be collected by the IRS and will raise \$6.9 billion in 2016. Part of this money will go toward government aid programs to help middle-class and low-income households afford healthcare coverage.

The Act provides exemptions for low-income people in states that opt out from major Medicaid expansion, and for people with financial hardships, religious objections and certain other circumstances. More than 150 million people are currently covered by employer plans, government programs such as Medicare or private individual policies; therefore, most Americans will not have to worry about the requirement since they are already insured. ❖

CARLA SCHICK is a staff writer for BioSupply Trends Quarterly.

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

Which billing codes would a home infusion provider use to seek reimbursement for Hizentra, including supplies, pump and nursing, for a primary immunodeficiency disease?

The Healthcare Common Procedure Coding System (HCPCS) is the national standard coding that defines and often combines medically necessary items billed by a provider. Coding of the supplies and pump are different for Medicare compared with other commercial insurance carriers.

Under Medicare, Hizentra 20% liquid (immune globulin subcutaneous) is covered by the External Infusion Pump LCD (local coverage determination) policy for Part B Medicare patients who have one of the following diagnoses: 279.04 (congenital hypogammaglobulinemia), 279.05 (immune deficiency with increased IgM), 279.06 (common variable immune deficiency), 279.12 (Wiskott-Aldrich syndrome) or 279.2 (combined immunity deficiency). The therapy must be administered with a Freedom 60 Pump (the only pump that Medicare will consider) with an HCPCS code of E0779.

The drug Hizentra is billed with a J1559 (injection, immune globulin [Hizentra] 100 mg) (HCPCS Level II, 2011). To calculate the number of units billed, a provider would convert the number of grams to milligrams (mg) (1 gram=1,000 mg) and then divide by 100. For example, for a patient who infuses 7 grams per week or 28 grams per month, a provider would bill for a total quantity of 280 mg for the month. In addition to the pump and drug, a provider would bill Medicare for supplies dispensed with a kit code (K0552: supplies for external drug infusion pump, syringe type cartridge, sterile, each) and a code for infusion sets and all other supplies (A4221: one per week).



If a patient meets all criteria, Medicare will pay 80 percent of the fee schedule, and the patient or secondary/supplemental insurance will be responsible for the remaining 20 percent. Nursing would be covered only if a patient meets the homebound status. If a patient meets this status, a Medicare Certified Nursing Agency would provide nursing services and bill Medicare Part A, which would cover 100 percent of the cost.

Under commercial insurance carriers, providers have found that each carrier and/or plan may use different criteria when it comes to its medical guidelines for subcutaneous immune globulin (SCIG). Carriers often will publish these guidelines on their websites, making it convenient for providers to obtain this information and compare it with the medical documentation obtained from the referring physician.

When billing commercial insurance carriers, the methodology is slightly

different from what it is with Medicare. Most companies recognize the national standard coding and utilize the per-diem codes. For SCIG, the most appropriate per-diem code is S9338. The HCPCS definition of this code is “home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment, drugs and nursing visits coded separately, per-diem” (HCPCS Level II, 2011). This per-diem code can be billed for each day a patient infuses unless otherwise noted in a provider’s contract with a payer. The average reimbursement for per diems for SCIG can range from \$30 to \$75 a day. For instance, if a patient infuses 7 grams of Hizentra per week, the total number of per diems billed within the month would be four.

As described in the per-diem definition, all supplies, pharmacy services, delivery and coordination are included within this code. Nursing should be billed separately. Standard nursing codes for home infusion consist of 99601 (home infusion/specialty drug administration, per visit, up to 2 hours) and 99602 (each additional hour) (Current Procedural Coding Expert, 2011). For example, if a nursing visit is for three hours, a provider would bill for one 99601 code and one 99602 code. Common practice today is for a patient to be taught to infuse on their own within two to three teaching visits by a registered nurse.

For additional help with coding or reimbursement questions, physicians and providers can call the IGIQ Resource Center at (877) 355-IGIQ (4447). ❖

What is the new clotting factor furnishing fee reimbursement rate for 2013?

The Social Security Act, added by the Medicare Modernization Act Section 303(e)(1), required, beginning Jan. 1, 2005, that a clotting factor furnishing fee be paid separately when furnishing clotting factor unless the costs associated with furnishing the clotting factor are paid through another payment system. The Centers for Medicare and Medicaid Services includes the clotting factor furnishing fee in the published national payment limits for clotting factor billing codes. When the national payment limit for a clotting factor is not included on the average sales price (ASP) Medicare



Part B drug pricing file or the not otherwise classified (NOC) drug pricing file, the carrier, fiscal intermediary, regional home health intermediary or A/B Medicare administrative contractor must make payment for the clotting

factor, as for the furnishing fee.

According to change request 8049, for the calendar year 2013, the clotting factor furnishing fee of \$0.188 per unit is included in the published payment limit for clotting factors. For dates of service in 2013, the clotting factor furnishing fee of \$0.188 per unit is added to the payment when no payment limit for the clotting factor is included in the ASP or NOC drug pricing files.

The official change request 8049 can be viewed at www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R2554CP.pdf. ❖

What are the updated payment allowances for seasonal influenza virus vaccines?



The Centers for Medicare and Medicaid Services provides payment allowances for seasonal influenza virus vaccines when payment is based on 95 percent of the average wholesale price (AWP) (except when payment is based on reasonable cost where the vaccine is furnished in a hospital outpatient department, a rural health clinic or a federally qualified health center). According to change order 8047, payment allowances have been updated effective Aug. 1, 2012.

Payment allowances are provided for the following current procedural termi-

nology (CPT) codes: 90654 (\$18,981), 90655 (\$16,456), 90656 (\$12,298), 90657 (\$6,023), 90660 (\$23,456) and 90662 (\$30,923). Payment for CPT codes 90654 (flu vaccine, intradermal, preservative free [Fluzone ID]), 90660 (FluMist, a nasal influenza vaccine) or 90662 (Fluzone High-Dose) may be made only if the local claims processing contractor determines its use is medically reasonable and necessary for the beneficiary.

Payment allowances also are provided for the following Healthcare Common Procedure Coding System (HCPCS) codes: Q2034 (Agriflu), Q2035 (Afluria, \$11,543), Q2036 (Flulaval, \$9,833), Q2037 (Fluvirin, \$14,051), Q2038 (Fluzone, \$12,046) and Q2039 (flu vaccine adult, not otherwise classified). The payment allowance for Q2034 and Q2039 will be determined by the local claims processing contractor.

Payment allowances for pneumococcal vaccines are updated on a quarterly basis via the quarterly average sales price drug pricing files.

For all payment allowances, annual Part B deductible and co-insurance amounts do not apply. All physicians, non-physician practitioners and suppliers who administer the influenza virus vaccines and pneumococcal vaccines must take assignment on the claim for the vaccine. In addition, Medicare contractors will not search their files to either retract payment for claims already paid or to retroactively pay claims. However, contractors will adjust claims brought to their attention.

The official change request 8047 instruction can be viewed at www.cms.hhs.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R2555CP.pdf. ❖

Ask Our Experts

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

Research

Scientists Discover How/When Infection Triggers Autoimmune Disorders

A team of researchers at the Garvan Institute of Medical Research in Sydney, Australia, have identified a weak link in the immune system and “the exact conditions under which an infection can trigger an autoantibody response.” According to the researchers who specialize in the study of how immune B cells produce self-attacking rogue antibodies, their finding “explains a lot about how autoimmune conditions that target particular organs such as the heart or nervous system could develop after an infection.”

Immune cells go through processes when they are first formed that ensure they are able to identify self and, therefore, avoid self-attack. But the antibody-creating B cells go through a second phase of development when the body is engaged in trying to fend off disease or infection. To cope with the immeasurable range of microbes in our environment, B cells have evolved the ability to mutate their antibody genes randomly until they produce one that sticks strongly to the invader. At that point, the successful B cells proliferate and flood the system with these new antibodies. This



“high affinity antibody” generation process occurs rapidly within specialized environments in the lymph system known as germinal centers. Most of the time, germinal centers help fight disease and build up a protective armory for the future. But the urgency and speed at which B cells mutate within the germinal center, as well as the random nature of the process, sometimes creates an antibody that also happens to match self and has the potential to cause autoimmune activity.

The researchers, who developed sophisticated mouse models to investigate when and how this happens, found that when the invading antigen is abundant and generally present throughout the body, rogue autoantibody-generating B cells are deleted and autoimmunity is avoided. But when the target antigen is located only in a tissue or organ remote from the germinal center, B cells capable of reacting against both antigen and self are able to escape the germinal center and produce autoantibodies. Essentially, the researchers say they’ve shown there’s a hole in self-tolerance when it comes to cross-reactive autoantibodies that can attack organ-specific targets. Their findings suggest that if enough is known about the disease and the molecular messaging systems involved, it may be possible in the future to modulate the germinal center response. They plan to continue to use their new mouse model to study the various molecular reactions involved in the progression of an autoimmune response.

The study was published in the November 8 edition of the journal *Immunity*. ❖

Insurance

48,000 Preventable Deaths in 2011 Due to Lack of Insurance

Approximately 48,000 people died in the U.S. in 2011 because they couldn’t get access to timely and appropriate medical care. The estimated death toll is based on a peer-reviewed Harvard study published in the *American Journal of Public Health* in 2009, which was widely cited during the healthcare reform debate, that found for every one million persons who were uninsured, there were about 1,000 related, preventable deaths. This is despite the slight drop in the year’s total number of uninsured — 46.8

million from a record 50 million in 2010 — that is largely attributable to an increase in government health insurance coverage, particularly persons covered by Medicaid and Medicare.

Studies have shown that uninsured people with chronic illnesses like heart disease delay or forgo care, often leading to serious complications of their medical condition and, in many cases, premature death, according to Dr. Steffie Woolhandler, professor of public health at the City University of New York, visiting

professor of medicine at Harvard Medical School and co-author of the Harvard study. “As a physician, I simply cannot accept a situation where tens of thousands of people die every year because they lack insurance coverage,” said Dr. Woolhandler. “And lest anyone think this problem has been solved by the federal health law, the Congressional Budget Office estimates about 30 million people will still be uninsured in 2022. We should adopt a zero-tolerance policy toward lack of health coverage.” ❖

Manufacturers

CSL Wins U.S. Government Contract for Flu Vaccines

CSL Biotherapies, a subsidiary of CSL Limited, has won a supply contract for pre-pandemic and pandemic vaccine antigens and related services to the U.S. national stockpile from the U.S. Department of Health and Human Services. The contract has a maximum potential value of \$1,511,407,737.78 if all optional activities are exercised over the duration of the contract. Under the terms of the contract, the government may request CSL to manufacture and store bulk antigen that can be used against influenza strains with pandemic potential, to develop working virus seeds for other manufacturers and to formulate, fill and finish bulk stored antigen. ❖

Research

Niacin Could Stop Spread of MRSA

In a recent study, scientists found that high doses of niacin, or vitamin B3, massively boost the body's defenses against staphylococcus bacteria. In tests of mice and human blood samples, large doses of niacin increased the numbers of neutrophils, specialized white blood cells that kill and eat harmful bacteria. By doing so, the immune system's ability to kill different strains of antibiotic-resistant superbugs, including methicillin-resistant *Staphylococcus aureus* (MRSA), was increased up to 1,000 times. However, the researchers used clinical megadoses of niacin far beyond what any normal diet would provide, but similar to those previously given to patients undergoing treatment.

"Antibiotics are wonder drugs, but they face increasing problems with resistance by various types of bacteria, especially *Staphylococcus aureus*," said lead researcher Dr. Adrian Gombart



from Oregon State University. "This could give us a new way to treat staph infections that can be deadly, and might be used in combination with current biotics. It's a way to tap into the power of the innate immune system and stimulate it to provide a more powerful and natural immune response." The research was published in the August 28 edition of the *Journal of Clinical Investigation*. ❖

Research

Flu and Fever in Pregnancy Is Linked to Autism Risk



A new study shows that children whose mothers had the flu or ran a fever lasting more than a week during pregnancy had an increased risk of developing

an autism spectrum disorder. The study analyzed data collected from 97,000 mothers of children born from 1997 through 2003 and found that while there was no association between mothers who reported common respiratory or sinus infections, common colds, urinary tract or genital infections during pregnancy and autism in their children, those whose mothers reported influenza during pregnancy had twice the risk of being diagnosed with autism before age 3, and those whose mothers had a fever for more than seven days had a three-fold risk. There also was a small increased risk of autism after the mother's use of various antibiotics during pregnancy, although the study did not specify the conditions for which the antibiotics were prescribed.

U.S. health officials caution that the new study is exploratory and does not

offer a specific cause of the developmental disability. "The study is really exploratory, and more research needs to be done to understand how maternal infections, as well as other risk factors, influence the risk of autism spectrum disorders," says Coleen Boyle, director of the Centers for Disease Control and Prevention's (CDC) National Center on Birth Defects and Developmental Disabilities. "We need to have more information to get a better sense of what's going on here." Therefore, says Marshalyne Yeargin-Allsopp, chief of the CDC's Developmental Disabilities branch, for now, the standard clinical recommendations for treating pregnant women suffering from fever or flu should not change as a result of this new preliminary finding.

The study was published in the November 12 issue of *Pediatrics*. ❖

Research

Pertussis Vaccine Loses Power Over Time



A new study suggests that protection from the childhood series of the diphtheria, tetanus and acellular pertussis (DTaP) vaccine fades within five years of the final dose. The study, published in the *New England Journal of Medicine*, involved data from 2006 to 2011 on children in Northern California who received a fifth dose of DTaP between the recommended ages of 4 and 6. Of those children, 277 had a positive PCR test for pertussis, 3,318 had a negative PCR test and 6,086 matched controls who were not tested for the disease. The researchers found that a larger period of time from the fifth dose of the vaccine was linked to a higher percentage of positive PCR tests, with 0.8 percent of the tests coming up positive when they were conducted 15 days to one year after the last dose and 18.5 percent testing positive six to eight years after the fifth dose. “This is an important paper, as it adds to our understanding of the waning immunity with DTaP vaccine,” said Dr. Mark Sawyer, chair of the pertussis vaccines working group for the Advisory Committee on Immunization Practices. “Although the current vaccines are less than perfect, they are all we have to protect the population from pertussis.” ❖

Medicines

Baxter Receives FDA Approval for Advate 4000 IU

Baxter International has received U.S. Food and Drug Administration (FDA) approval for a 4,000 IU dosage of Advate (Antihemophilic Factor [Recombinant], Plasma/Albumin-Free Method). Advate is meant for the avoidance or curtailment of bleeding in victims of hemophilia A. The latest 4,000 IU dose provides the ease

of a single dosage for many patients.

Last December, Advate received FDA approval as a regular prophylaxis to curtail the incidence of bleeding for patients with hemophilia A. It thus became the sole antihemophilic recombinant FVIII therapy approved in the domestic market for use by both children and adults. ❖

Research

Scientists Closer to a Universal Flu Vaccine

Recent studies of the flu virus are bringing hope that seasonal flu vaccines will be replaced with long-lasting universal vaccines. Currently, flu vaccines are updated each year with three and soon-to-be four of the most prevalent circulating virus strains. They protect people from the virus strains by letting them make antibodies in advance. The vaccines contain fragments from the tip of a protein on the surface of the virus, called hemagglutinin, B cells that encounter the vaccine fragments and learn how to make antibodies against them. Therefore, these vaccines can protect against only flu viruses with a matching strain.

Dr. Sarah Gilbert and her colleagues at Oxford University are trying to build a T cell-based vaccine that could attack a part of the flu virus that changes little from year to year. They’ve found that when T cells learn to recognize proteins from one kind of virus, they can attack many other kinds. It appears that the flu proteins that infected cells select to put on display evolve very little. The scientists are testing a vaccine that prepares T cells to mount a strong attack against flu viruses by engineering a virus that can infect cells but cannot replicate. As a result, infected cells put proteins on display, but people who receive the vaccine do not get sick. In a clinical trial, 11 vaccinated individuals and 11 unvaccinated individuals were given the vaccine and then exposed to the



flu. Two of the vaccinated people became ill, while five unvaccinated ones did.

While the Oxford researchers are focusing on T cells, other researchers are developing vaccines that can generate antibodies that are effective against many flu viruses, or perhaps all of them. The goal, according to Gary J. Nabel, director of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases, is for individuals to receive two shots when they are young and then boosters later in life.

A universal vaccine would not only help in the fight against seasonal flu outbreaks, but Dr. Gilbert argues that it could potentially have greater benefit for protection against pandemic flu viruses. Currently, scientists don’t have a vaccine for a new pandemic strain until an outbreak is well under way. An effective universal vaccine would already be able to fight it. ❖



Research

Third Dose of MMR Vaccine May Help to Control Mumps Outbreak

In a recent study, researchers tested a third dose of the measles-mumps-rubella (MMR) vaccine on students in an affected community in an effort to control the outbreak. In the study, 2,178 sixth- to 12th-grade students in three schools with proof of having received two previous doses of MMR vaccine were offered a third dose of the vaccine and monitored to assess mumps attack rates. The overall attack rate for all students declined from 3.93 percent in the prevaccination period to 0.13 percent after vaccination. Overall

in the affected area, the attack rate declined by 75.6 percent after the intervention. And, while a decline occurred in all age groups, it was significantly greater (96 percent) among 11- to 17-year-olds, the age group targeted for vaccination, than among all other age groups. The researchers concluded that a third dose of the MMR vaccine may help control mumps outbreaks among populations with pre-existing high two-dose vaccine coverage. The study was published in the November 5 edition of *Pediatrics*. ❖



Vaccines

Meningitis B Vaccine Shows Promise



Researchers have concluded a Phase II study of an investigational vaccine against group B *Neisseria meningitidis*, which shows promising results. The bivalent vaccine uses lipoprotein 2086, a surface-exposed and immunogenetic factor H binding protein that is present in at least 98 percent of all meningococcal group B strains, as well as in an equal number of variants from families A and B.

In the study, 589 adolescents from 25 sites across Australia, Poland and Spain were randomly assigned to receive one of three vaccine doses (60 µg, 120 µg, or 200 µg) or a placebo injection administered at zero, two and six months; 511 participants received all three doses. Results showed that all three doses produced an immune response in 80 percent to 100 percent of participants, depending on the dose and strain tested. The 120-µg and 200-µg vaccine doses

were similarly effective.

Mild to moderate injection site pain was common and occurred more frequently among participants receiving the vaccine, lasting a mean of two to three days. The most common systemic events were mild to moderate fatigue, fever and headache that lasted one to three days. However, adverse event incidence and severity did not increase with subsequent vaccinations. Only one serious adverse event was considered related to the study vaccine: A boy aged 13 years experienced a sudden severe headache and vomiting within an hour of the third dose.

“Our data suggest that this vaccine is a promising and broadly protective meningococcal serogroup B vaccine candidate.... If additional studies show similar immunogenicity and tolerability, this vaccine might help to reduce the global burden of invasive meningococcal disease,” wrote lead author Peter Richmond, MBBS, from the University of Western Australia School of Paediatrics and Child Health, Vaccine Trials Group, Telethon Institute for Child Health Research, Princess Margaret Hospital for Children, Subiaco and colleagues. The study was published online on May 7, 2012, in the journal *The Lancet*. ❖

Vaccines

Experimental Prostate Cancer Vaccine Shows Promise

Metastatic prostate cancer patients who received an investigational vaccine made from their own frozen immune cells lived 10 months longer than those not treated with it, according to data presented by researchers at the Kimmel Cancer Center at Jefferson.

In an explanatory, multi-institutional analysis, researchers administered the vaccine APC8015F to a group of patients from the control arm of three randomized Phase III clinical trials evaluating sipuleucel-T (Provenge), a similar FDA-approved cancer vaccine for metastatic castrate-resistant prostate cancer. APC8015F is made from immune system cells taken from a patient with prostate cancer. However, unlike sipuleucel-T, which is never frozen, APC8015F is cryopreserved at a time before the disease progresses. Results from the analysis showed that patients treated with APC8015F had improved survival relative to the patients who were not treated in the control arm. Following disease progression, the median survival of patients treated with APC8015F was 20 months compared with 9.8 months for control patients. ❖

People and Places in the News

CLINICAL TRIALS

Researchers at the **University of California, San Francisco** are conducting a clinical trial to test the vaccine **Provenge** for the prevention of prostate cancer. Currently, the vaccine is only being used to treat people who have recently been diagnosed with prostate cancer and are planning to undergo surgery.

Results from the first clinical trial of **Sanaria's** experimental **malaria** vaccine resulted in only five of the 80 vaccinated volunteers being protected from infection.

Merrion Pharmaceuticals is conducting a Phase III study for **Orazol**, a weekly tablet bisphosphonate (zoledronic acid) compound for the treatment of early stage breast cancer and metastatic bone disease. If successful, a new drug application will be made under the FDA's abbreviated approval procedure.

A Phase III clinical trial conducted by **sanofi-aventis** and its subsidiary, **BiPar Sciences**, to evaluate **iniparib** (BSI-201) in patients with metastatic triple-negative breast cancer did not meet the prespecified criteria for significance for co-primary endpoints of overall survival and progression-free survival.

Plexxikon Inc. has begun its first of two Phase I clinical trials with **PLX5622**, a novel, oral and highly selective Fms inhibitor, targeted for the treatment of rheumatoid arthritis. PLX5622 has been shown in preclinical arthritis models to reduce inflammation, reduce cartilage damage and prevent bone resorption.

Baxter has begun a Phase I prospective, open-label study that will assess

the safety, tolerability and pharmacokinetics of its lead investigational candidate, BAX 855, a longer-acting (PEGylated) form of a full-length recombinant factor VIII (rFVIII) protein, in previously treated patients aged 12 years or older with severe **hemophilia A**. When used for prophylaxis, Baxter's Advate requires patients to infuse every two to three days to reduce the occurrence of bleeding episodes. This Phase I trial is the first step in assessing whether BAX 855 can be infused less frequently.

Baxter has begun a second Phase III clinical trial of its Gammagard Liquid 10% Immune Globulin Infusion (Human), which is marketed as Kiovig outside the U.S. and Canada, for the treatment of mild to moderate **Alzheimer's** disease. This second Phase III trial is identical in design to the first, and it will assess the safety and effectiveness of Gammagard Liquid as a potential treatment for signs and symptoms associated with Alzheimer's disease.

Neovacs has announced the full results for its TNF-K-003 clinical trial with TNF-Kinoid in **rheumatoid arthritis**. According to the company, the results confirm the very good safety profile of TNF-Kinoid. No patient withdrew from the study because of an adverse event, and no serious Kinoid-related adverse events were reported.

Trubion Pharmaceuticals has started a clinical trial of a drug for **lupus**. SBI-087 is made to hit a target called CD20, which is currently blocked by Genentech and Biogen Idec's rituximab (Rituxan) for patients with a different form of autoimmune disease, rheumatoid arthritis. The Trubion drug, which is also being tested for rheumatoid arthritis, is being developed

in partnership with Madison, N.J.-based Wyeth.

Researchers at the **Roswell Park Cancer Institute** in Buffalo, N.Y., have begun a Phase I clinical research study of a **cancer** vaccine that they say harnesses the power of the body's immune system to kill cancer cells. The dendritic cell vaccine will be manufactured in a specially designed production unit approved by the U.S. Food and Drug Administration and will be given in combination with a compound found to prolong its effectiveness. About 18 to 20 patients with various types of cancers will take part in the study.

MediGene AG has begun a clinical trial of its drug candidate RhuDex to develop an optimized oral formulation of the active substance suitable for the treatment of **chronic diseases**. The results of this formulation study are expected midyear 2012.

BiondVax Pharmaceuticals has had positive results with its second Phase II clinical trial of the **universal influenza vaccine**, Multimeric-001 for improving existing flu vaccines in the elderly. The vaccine was found to be safe and well-tolerated, and induced robust cellular and humoral immune responses in patients 65 and older. In addition, when given as a primer before boosting with a seasonal trivalent influenza vaccine (TIV), Multimeric-001 enhanced the performance of that vaccine by increasing immunity to influenza strains contained in the TIV.

CSL Behring has initiated a Phase I study with rVIIa-FP, a novel therapy to treat people with **hemophilia A** and **hemophilia B** who have inhibitors. The study will evaluate the safety and pharmacokinetics of rVIIa-FP, in



comparison to a placebo, in healthy volunteers.

Idera Pharmaceuticals Inc. has announced that results of a randomized, controlled Phase II clinical trial of IMO-2055, an investigational oncology product candidate targeting toll-like receptor 9 in combination with Erbitux (cetuximab) for the treatment of recurrent or **metastatic squamous cell carcinoma** of the head and neck (SCCHN) in patients who previously progressed on chemotherapy, did not meet its primary endpoint of improved progression-free survival compared with treatment with cetuximab alone.

Neovacs' Phase II clinical study TNF-K-005 in patients with **Crohn's disease** who have failed therapy with at least one anti-TNF monoclonal antibody did not show any statistically significant difference in terms of clinical remission between the Kinoid-treated group and the placebo group. However, it did demonstrate a statistically significant correlation between clinical remission and the level of antibodies induced by the Kinoid, which confirms the biological activity of the Kinoid. Specifically, in the Kinoid group, the patients achieving remission are those with the highest level of anti-TNF antibodies induced by the Kinoid. In addition, it showed a major factor explaining nonresponse to the Kinoid is the ongoing presence of monoclonal antibodies at the time of entry into the study. And, it demonstrated the excellent safety profile of the TNF-Kinoid, consistent with the two previous studies. All these findings are subject to confirmation in the final phase of the study, results from which were scheduled to be published in the fourth quarter of 2012.

Research

Vaccine to Prevent Premature Birth May Be Possible

New research suggests it might someday be possible to create a vaccine that could protect a growing fetus from premature birth and related complications. The key: CD4 T cells. According to the study's authors, fetal tissue contains material inherited from both the mother and the father, which raises the risk that the mother's immune system may recognize the fetus as a foreign invader that must be rejected. When a woman becomes pregnant, her immune system stimulates CD4 T cells, which create a rejection roadblock to stop the mother's immune system from attacking fetal tissue so there is a successful pregnancy. In addition, they found that the CD4 T cells have a so-called memory feature that means, once induced into action during a woman's first pregnancy, these cells tend to perform their immune system-suppression task even better during subsequent pregnancies. This, they said, would explain why the



risk for complications and premature birth goes down after a first pregnancy.

The researchers believe their findings are a blueprint that might lead to a vaccine that could better ensure that mothers can carry their babies to term. So far, the investigators' research for a possible vaccine has been limited to work involving mice. The research was supported by grants from the U.S. National Institutes of Health. ❖

Research

Vitamin D Activates Immune Response to TB

A new study shows that vitamin D is needed to activate the immune system's response to tuberculosis (TB). Published in *Science Translational Medicine*, the study shows that vitamin D is necessary for the T cells, which respond to threats as part of the body's adaptive immune system, to produce a protein called interferon that directs cells to attack the bacteria. Previous studies by the same research team found that vitamin D played a key role in producing a molecule called cathelicidin, which helps the innate immune system kill the TB virus. "At a time when drug-resistant forms of tubercu-

losis are emerging, understanding how to enhance natural innate and acquired immunity through vitamin D may be very helpful," says Barry Bloom, former dean of the faculty at the Harvard School of Public Health and co-author of the study.

The findings could lead to new treatments for the lung disease that kills 1.8 million people per year. They also could be crucial to treat the disease in parts of the world like Africa, since people with dark skin tend to be more susceptible to TB and also are more likely to have vitamin D deficiencies. ❖

Education

Immunoglobulin Nursing Society Holds First National Conference



The Immunoglobulin Nursing Society (IgNS) held its first national conference in Orlando, Fla., August 3 through 5. The conference is a new educational initiative to develop and sustain the advancement of knowledge, education and practice of nursing in the field of immunoglobulin (IG) therapy. It featured in-depth educational sessions, hands-on practical workshops, industry-sponsored symposia and an exhibit hall featuring the top IG-related companies in the country.

Educational sessions included the latest developments in the field of IG therapy, including clinical indications, administration and adverse event prevention and management, updates on the IG clinical trial landscape and the role of nurse study coordinators, as well as an update on issues with IG reimbursement and patient advocacy. Several smaller group practical workshops were taught by leading IG nurse experts focusing on best practices in intravenous IG (IVIG) and subcutaneous IG (SCIG) administration.

“The IgNS National Conference represents a major shift in the current education and training of IG nurses who treat patients with chronic and life-threatening disorders,” said Jane Kirmse, RN, MSN, APRN-BC, president of IgNS. “The National Conference will provide nurses with an exceptional educational program to expand their knowledge, advance their skills and experience professional growth.” ❖

Vaccines

Swine Flu Vaccine May Protect Against Other Flu Viruses

Researchers at the University of British Columbia (UBC) have found that the swine flu vaccine triggers antibodies that protect against many flu viruses, including the lethal bird flu strain. According to UBC Professor John Schrader, the findings support the idea that there is a way to develop universal flu vaccines that would eliminate the need for seasonal vaccines each year.

Schrader compared virus proteins with a tulip-like structure. Whereas

traditional vaccines adhere to the “flower head” of the structure, which mutate regularly and require new vaccines, the swine flu vaccine appeared to produce antibodies that attacked the “stem” of the flu virus proteins, creating more stable resistance. “The stem plays such an integral role in penetrating the cell that it cannot change between different variants of the flu virus,” said Schrader.

The research was published May 8 in the journal *Frontiers in Immunology*. ❖

Vaccines

CDC Preparing Vaccine for New Swine Flu



Despite only 29 human cases of the new strain of swine flu in the past two years, the Centers for Disease Control and Prevention (CDC) is preparing an H3N2 candidate vaccine, and clinical trials are being planned for this year.

The CDC is concerned about this virus because it contains an element seen in the pandemic 2009 swine flu strain, H1N1, which may make it more likely for the virus to spread from person to person. All 29 cases were infected with strains of H3N2 “that contained the matrix (m) gene from the influenza A H1N1 pandemic virus,” explained Dr. Joseph Bresee, from the CDC’s influenza division. “This m gene may confer increased transmissibility to and among humans, compared with other variant influenza viruses.” In addition, the virus appears to have become more active recently, with 16 of the 29 cases diagnosed in July. Of the 16 new cases, 13 arose in children. Studies indicate that children may be more sus-

ceptible to the infection than adults, as occurred during the 2009-2010 pandemic H1N1 flu outbreak, said Bresee.

Flu viruses commonly circulate in pigs, but they are generally different from those that spread to people. However, when someone comes into close contact with an infected animal, these viruses can sometimes spread to people. All of the recent 16 cases were among people who had direct contact with pigs. In 15 cases, contact happened at a county fair. “Swine influenza viruses have not been shown to be transmissible to people through eating or handling pork or other products derived from pigs. It is not a food-borne disease,” Bresee said.

No human-to-human transfer of the virus occurred in the more recent cases, Bresee said, although scientists did find evidence of limited human-to-human transmission in three cases in 2011. And, fortunately, sustained person-to-person transmission of the virus hasn’t happened yet. To prevent contracting this flu, the CDC advises people to limit their contact with swine and avoid contact with sick swine. People who have contact with these animals should take precautions such as washing their hands, not eating or drinking in areas with swine and controlling their cough. ❖



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When It Turns Out to Be Primary Immunodeficiency Disease: **Benefits of Early Diagnosis**



Early referral for workup of patients with any of more than 150 occult primary immunodeficiency diseases can dramatically reduce hospitalizations, permanent disability and high costs of care.

By Keith Berman, MPH, MBA

Today in all 50 states in the U.S., every newborn is screened for cystic fibrosis with a genetic test or blood test so that treatment can begin almost immediately. The unusual excessive bleeding in infants or young children with hemophilia generally leads to a prompt referral to a hematologist and coagulation testing to identify the disorder. But for the more than 150 distinct genetically-based primary immunodeficiency diseases (PIDDs) characterized to date, nor for most are there any readily recognizable clinical manifestations.

For all but the most severely affected individuals, PIDD typically manifests as “ordinary” infections, most often involving the ears, lungs or sinuses. Consequently, it often takes years for infants born with a PIDD to be diagnosed and to start receiving immune globulin (IG) prophylaxis or other disease-appropriate therapy. In the meantime, repeated unusually severe or prolonged infections place many of these individuals at risk for permanent organ damage or death.

The specific genetic immune system defect at fault may variously involve compromised function of T cells, phagocytic cells, complement or, in roughly half of all cases, B cells responsible for production of protective antibodies. While disease expression is at least as variable as the range of disorders themselves, this increased susceptibility to infection manifests as:

- high infection recurrence rate,
- unusual severity of infection,
- unusual persistence or complicated course,
- clinical infections with organisms of relatively low virulence.

At the far extreme is severe combined immunodeficiency (SCID), a group of 10 very rare genetic disorders characterized by profound deficits in both T and B cell function; SCID is frequently fatal without bone marrow transplantation. By

contrast, most patients with PIDD of mainly B cell origin have intact T cell immunity and some residual humoral immunity. The result is much variability in type, frequency and severity of mainly bacterial infections, but importantly a much less obvious serious infection history than one sees with SCID. With aggressive antibiotic therapy, patients usually recover, in effect further “masking” the underlying immune deficiency. But inevitably these patients are soon afflicted with a new infection or a recurrence of the same unresolved infection.

*It often takes years
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a PIDD to be diagnosed
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Under the Umbrella of PIDD

Immunologists have defined nine categories to broadly classify the extraordinarily heterogeneous population of some 50,000 individuals labeled with the umbrella term “primary immunodeficiency.”¹ According to a recent U.S. provider

*Currently, at least 12 states (including California, Colorado, Connecticut, Delaware, Florida, Iowa, Massachusetts, Michigan, Mississippi, New York, Texas and Wisconsin) test for severe combined immunodeficiency using T-cell receptor excision circle (TREC) assays, which identify infants with absent or extremely low numbers of T cells.

survey that captured 15,600 U.S. patients, the PIDD population is distributed among these disorders as follows:²

- Combined T- and B-cell immunodeficiencies: 3.9%
- Other well-defined immunodeficiency syndromes: 21.9%
- Diseases of immune dysregulation: 1.8%
- Congenital defects of phagocyte numbers and function: 2.9%
- **Predominantly antibody deficiencies: 53.8%**
- Defects in innate immunity: 0.8%
- Autoinflammatory disorders: 2.3%
- Complement deficiencies: 3.6%
- Other immunodeficiencies: 9.1%

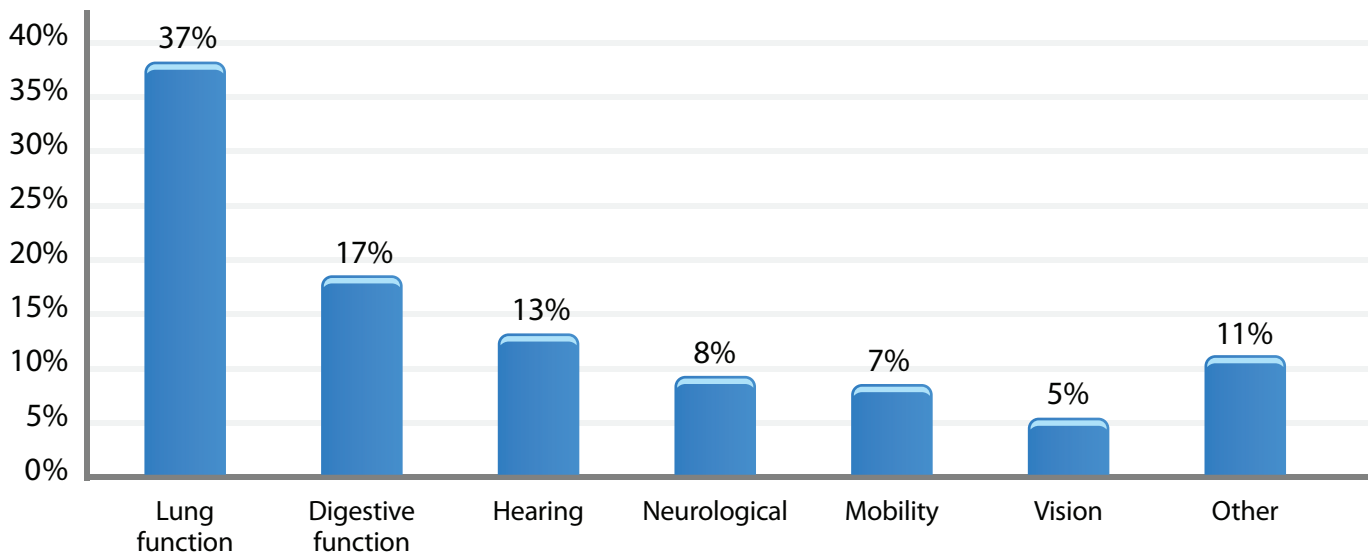
Common variable immunodeficiency (CVID) disorders account for most of the roughly one-half of persons whose condition predominantly involves antibody deficiencies. These individuals have severe reductions in serum IgG and IgA, with normal, low or very low numbers of B cells. Their deficient IgG antibody production in particular puts them at high risk for recurrent bacterial infections. Depending on the specific genetic disorder, the underlying problem may be a deficiency in total Ig concentrations, or a significant inability to respond with IgG antibody production after an antigenic challenge (typified by a lack of response against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine or both).

For CVID and certain other disorders involving impaired antibody production, adequate replacement with IVIG or subcutaneous IG (SCIG) has been shown to reduce the incidence of pneumonia and prevent the progression of lung disease.³ A recent meta-analysis of 17 clinical trials evaluating



a total of 676 patients found that pneumonia incidence declined 27 percent with each 100 mg/L increment in patients' trough IgG level just prior to the next IG administration. The incidence of pneumonia with maintenance of 500 mg/dL IgG trough levels was 0.113 cases per patient-year, five-fold higher than the incidence with maintenance of a trough level of 1,000 mg/dL — 0.023 cases per patient-year.⁴

Figure 1. Percentage of persons with PI (n = 1,030) reporting permanent impairments or losses prior to diagnosis⁸



Source: Immune Deficiency Foundation

After more than 30 years of experience, accumulating evidence has prompted recommendations to approach or exceed the lower limit of IgG concentration for normal healthy adults, which is approximately 700 mg/L.³

Beyond dosing to achieve a recommended target IgG trough level, one additional step in individualizing IgG replacement therapy is to adjust dosage upward, if and as needed, to minimize infection in that patient.

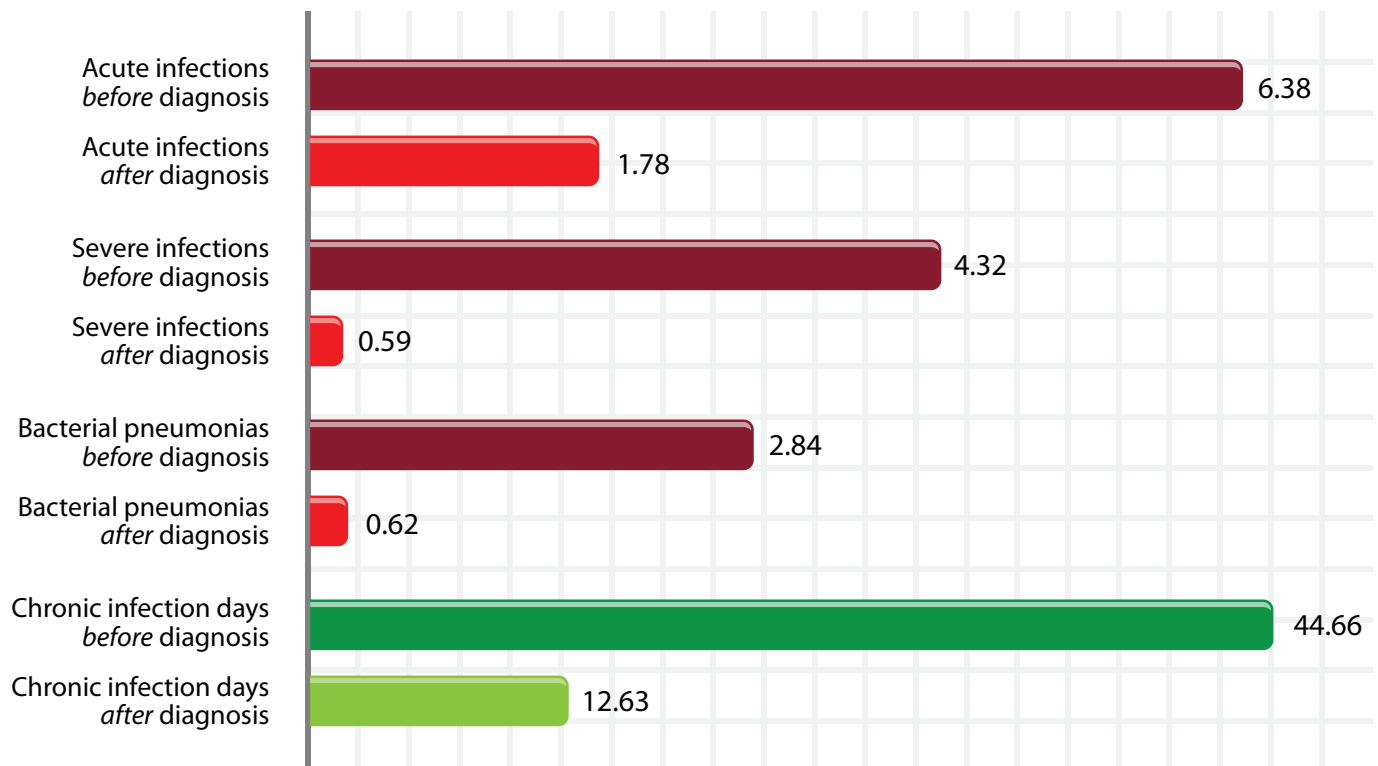
For some PIDD cases involving severe deficits in cell-mediated immunity, cellular therapy — most commonly hematopoietic stem cell transplantation — is the mainstay of treatment, with the goal of complete cure. Since the first bone marrow transplants for PIDD in 1968, stem cell transplantation for several life-threatening immunodeficiencies (including SCID) has enabled many hundreds of children with PIDD to live normal lives. Certain other patients, for example those with complete DiGeorge syndrome, benefit from thymus transplantation.⁵ In a highly promising recent study, a small number of X-linked SCID patients appear to have been cured with gene therapy.⁶

The biggest problem that persists with PIDD remains the years-long delay in diagnosing these individuals in the first place.

Health Status Before, After PIDD Diagnosis

But the biggest problem that persists with PIDD remains the years-long delay in diagnosing these individuals in the first place. Despite public outreach and dissemination of provider education materials, today many more than half of all persons

Figure 2. Infection experience in U.S. patients with PI during the year prior to and the year following diagnosis⁹



Source: Jeffrey Modell Foundation

with PIDDs are not diagnosed until they are adolescents or adults.⁷ According to a 2008 survey of more than 1,000 patients by the Immune Deficiency Foundation (IDF), the majority reported that they were hospitalized two or more times before a diagnosis was made, and about one-third were hospitalized four or more times.⁸ Nearly one in 10 were hospitalized with serious infections 11 or more times before their underlying PIDD disorder was finally diagnosed.

IDF survey respondents also reported that, not including hospitalizations, they were too sick to attend work or school or to perform their usual activities an average of 36.8 days during the 12 months prior to diagnosis. Nearly one in five missed more than a month, and 7 percent missed more than 100 days over the year prior to diagnosis. These and other indicators, in particular very high reported antibiotic days and physician visits, underscore the huge burden in morbidity and healthcare costs of undiagnosed PIDD.

Of particular concern are the permanent adverse effects of severe and repeated infections prior to diagnosis. Slightly more than half of patients surveyed by IDF reported permanent impairment or losses prior to their initial diagnosis, including 37 percent, 17 percent and 13 percent with permanent loss of lung function, digestive function and hearing, respectively (see Figure 1).

The Jeffrey Modell Foundation (JMF), an internationally acclaimed nonprofit organization that advocates for early diagnosis of PIDD, recently screened more than 60 million U.S. medical and drug insurance claims to isolate persons diagnosed with a PIDD and examined several key infection-related health parameters over the year prior to and the year following their diagnosis.⁹ Figure 2 presents a summary of those findings.

According to these data from JMF and academic collaborators,

the year following PIDD diagnosis is accompanied by dramatic declines in the number of severe infections (-86 percent), number of bacterial pneumonias (-78 percent) and days with chronic infections (-72 percent). All differences between the diagnosed and undiagnosed groups were highly significant ($P = 0.001$). Thus in a quantifiable fashion, these crude before-and-after findings powerfully demonstrate the importance of early diagnosis of the PIDD condition that can underlie severe, recurrent and persistent infections.

*Clearly, the responsibility
for earlier diagnosis of
PIDD ultimately resides
with each primary physician
who interfaces with
patients every day.*

The Cost of Treatment and Non-Treatment

In lock-step with those drops in infection rates following PIDD diagnosis are similar reductions in the number of physician/hospital/ER visits (-83 percent), hospitalization days (-74 percent) and days on antibiotics (-56 percent). Each directly translates, of course, into reduced costs (see Table 1).

Table 1. Selected estimated medical costs during the year prior to and the year following diagnosis of PIDD

	Annual cost per patient before diagnosis	Annual cost per patient post-diagnosis	Annual cost savings per patient
Physician/hospital/ER visits	\$11,875	\$1,977	\$9,899
Hospitalization	\$29,792	\$7,913	\$21,880
Antibiotics	\$946	\$414	\$532

Source: Jeffrey Modell Foundation

Altogether, the JMF investigators estimated total annual pre-diagnosis medical costs of \$138,760. Over the year following diagnosis, estimated medical costs plunged to just under \$30,300. For the roughly half of PIDD patients with primary humoral immunodeficiency, a very large annual savings remains even after the presumption of an additional \$30,000 annual cost for IG replacement therapy.

Working Toward Earlier Diagnosis

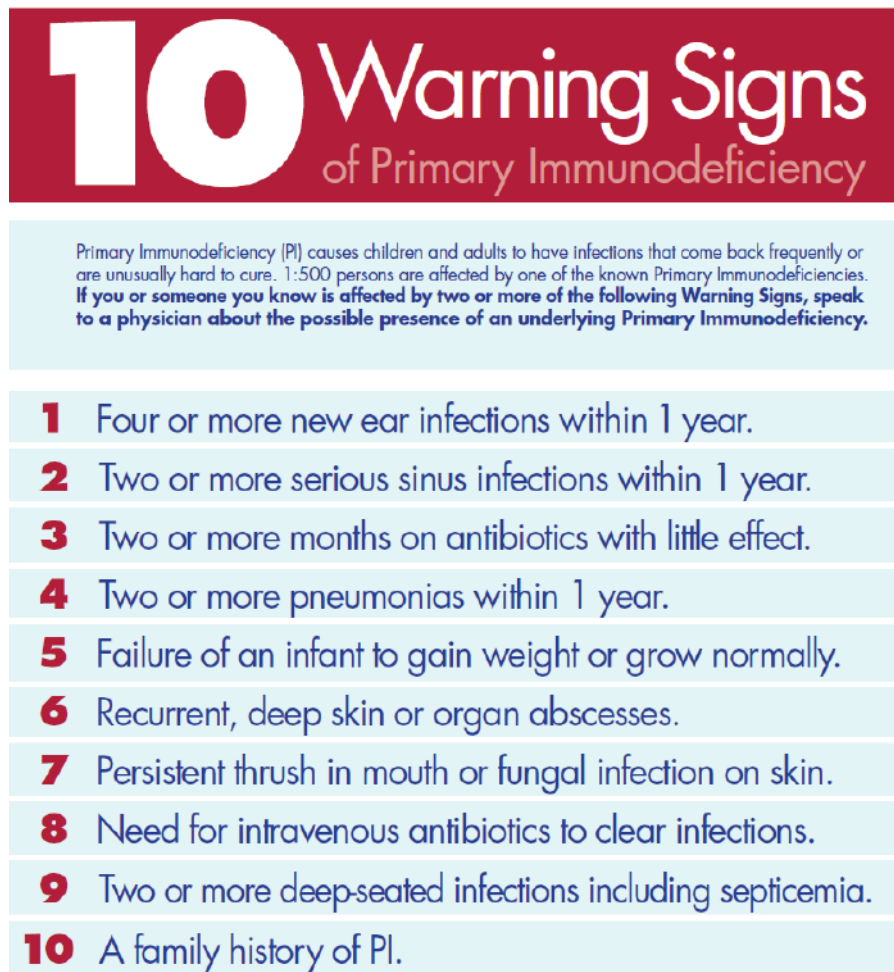
First developed in 1993 with support from the U.S. Centers for Disease Control and Prevention (CDC), JMF has disseminated a simple educational poster alerting physicians to the “10 Warning Signs of Primary Immunodeficiency” (see Figure 3).¹⁰ Various other educational materials — patient brochures, wall posters for school and day care facilities, public service announcements to reach the general public through television,

radio, print and the Internet — have and continue to be produced with funding support in part from the CDC and the National Institutes of Health. JMF reported more than 550,000 visits to its website last year and more than 23,500 calls to its information hotline.

But clearly the responsibility for earlier diagnosis of PIDD ultimately resides with each primary physician who interfaces with patients every day. Dr. Rebecca Buckley, a leading immunologist and researcher in this field, summed up the primary physician’s role quite nicely: “You need a high index of suspicion.” ❖

KEITH BERMAN, MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Since 1989, he has also served as editor of International Blood/Plasma News, a blood products industry newsletter.

Figure 3.



Source: Jeffrey Modell Foundation

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When treating a life-threatening bleed from **acquired hemophilia**, every second counts.



Indications and Usage

NovoSeven® RT (Coagulation Factor VIIa [Recombinant] Room Temperature Stable) is indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to FVIII or FIX and in patients with acquired hemophilia; prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to FVIII or FIX and in patients with acquired hemophilia; treatment of bleeding episodes in patients with congenital FVII deficiency and prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency.

Important Safety Information

Warning: Serious thrombotic adverse events are associated with the use of NovoSeven® RT outside labeled indications. Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven® RT have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven® RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

Thrombotic events following the administration of NovoSeven® RT occurred in 0.28% of bleeding episodes treated, with the incidence in acquired hemophilia of 4% and in hemophilia patients of 0.20% in clinical trials within the approved indications. Fatal and non-fatal thrombotic events have been identified through postmarketing surveillance following NovoSeven® RT use for each of the approved indications.

NovoSeven® RT is the only bypassing agent approved for acquired hemophilia¹

Count on NovoSeven® RT

For acquired hemophilia, NovoSeven® RT was 95% effective or partially effective as first-line therapy²

Data were extracted from a review of experiences with rFVIIa for the treatment of acquired hemophilia in compassionate-use programs, the Hemophilia and Thrombosis Research Society (HTRS) registry, and independent published reports. Efficacy was defined as “effective” and “partially effective” treatment outcomes. “Ineffective” treatment was determined by the inability to stop the bleeding episode or by the physician describing treatment as not effective.²

For Unique Billing Support Services

- Downloadable guide to coding and provider billing for NovoSeven® RT available at novosevenrt.com
- Healthcare Common Procedural Coding System (HCPCS) for NovoSeven® RT (1 mcg equivalent): **J7189³**



Talk to your authorized distributor to learn more about NovoSeven® RT or visit NovoSevenRT.com.

FFF Enterprises 1-800-843-7477

References:

1. NovoSeven RT [package insert]. Princeton, NJ: Novo Nordisk Inc; 2012. 2. Sumner JM, Geldziler BD, Pedersen M, Seremetis S. Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal. *Haemophilia*. 2007;13(5):451-461. 3. Centers for Medicare & Medicaid Services. 2011 HCPCS alpha-numeric index. <https://www.cms.gov/HCPCSReleaseCodeSets/Downloads/INDEX2011.pdf>. Updated November 4, 2010. Accessed August 22, 2012.

Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with activated or nonactivated prothrombin complex concentrates (aPCCs/PCCs) have an increased risk of developing thrombotic events in association with NovoSeven® RT treatment. Caution should be exercised when administering NovoSeven® RT to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, post-operative immobilization, elderly patients, and neonates. In each of these situations, the potential benefit of treatment with NovoSeven® RT should be weighed against the risk of these complications.

Development of antibodies against FVII has been reported in FVII-deficient patients after treatment with NovoSeven® RT. FVII-deficient patients should be monitored for prothrombin time (PT) and FVII coagulant activity before and after administration of NovoSeven® RT.

Use with caution in patients with known hypersensitivity to NovoSeven® RT, its components, or mouse, hamster, or bovine proteins.

Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis.

In clinical trials, the most common adverse events of NovoSeven® RT therapy are pyrexia, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema, and rash.

Please see brief summary of Full Prescribing Information on following pages.

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.

NovoSeven® RT is a prescription medicine. Novo Nordisk provides patient assistance for those who qualify.

Please call 1-866-310-7549 to learn more about Novo Nordisk assistance programs.

NovoSeven® RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable, Lyophilized Powder

Rx ONLY

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

Warning: Serious thrombotic adverse events are associated with the use of NovoSeven® RT outside labeled indications

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven® have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven® RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. **See WARNINGS AND PRECAUTIONS section of prescribing information.**

Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

INDICATIONS AND USAGE: NovoSeven® RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable is indicated for: Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia; Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia; Treatment of bleeding episodes in patients with congenital FVII deficiency; Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency

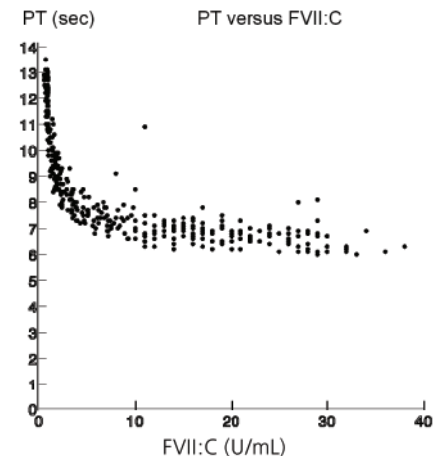
CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Thrombotic Events within the Licensed Indications: Clinical trials within the approved indications revealed that thrombotic events of possible or probable relationship to NovoSeven® occurred in 0.28% of bleeding episodes treated, with the incidence within hemophilia patients with inhibitors to be 0.20%, and in acquired hemophilia an incidence of 4%. Thrombotic events have been identified through postmarketing surveillance following NovoSeven® RT use for each of the approved indications. The incidence of thrombotic events can not be determined from postmarketing data. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or non-activated prothrombin complex concentrates) have an increased risk of developing thrombotic events due to circulating tissue factor (TF) or predisposing coagulopathy [See *Adverse Reactions*]. Caution should be exercised when administering NovoSeven® RT to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart

disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with NovoSeven® RT should be weighed against the risk of these complications. Patients who receive NovoSeven® RT should be monitored for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the NovoSeven® RT dosage should be reduced or the treatment stopped, depending on the patient's symptoms. **Thrombotic Events outside the Licensed Indications:**

NovoSeven® has been studied in placebo controlled trials outside the approved indications to control bleeding in intracerebral hemorrhage, advanced liver disease, trauma, cardiac surgery, spinal surgery, and other therapeutic areas. Safety and effectiveness has not been established in these settings and the use is not approved by FDA. Two meta analyses of these pooled data indicate an increased risk of thrombotic events (10.0% in patients treated with NovoSeven® versus 7.5% in placebo-treated patients). Arterial thromboembolic adverse events including myocardial infarction, myocardial ischemia, cerebral infarction and cerebral ischemia were statistically significantly increased with the use of NovoSeven® compared to placebo (5.3 to 5.6% in subjects treated with NovoSeven® versus 2.8 to 3.0% in placebo-treated patients). Other arterial thromboembolic events (such as retinal artery embolism, renal artery thrombosis, arterial thrombosis of limb, intracardiac thrombus, bowel infarction and intestinal infarction) have also been reported. While venous thromboembolic events such as deep venous thrombosis, portal vein thrombosis and pulmonary embolism have been reported in clinical trials, the meta analysis of these pooled data from placebo-controlled trials performed outside the currently approved indications did not suggest an increased risk of venous thromboembolic events in patients treated with NovoSeven® versus placebo (4.8% in patients treated with NovoSeven® versus 4.7% in placebo-treated patients). In spontaneous reports of women without a prior diagnosis of bleeding disorders receiving NovoSeven® for uncontrolled post-partum hemorrhage, thrombotic events were observed. During this period, patients are at increased risk for thrombotic complications. **Post-Hemostatic Dosing:** Precautions should be exercised when NovoSeven® RT is used for prolonged dosing. **Antibody Formation in Factor VII Deficient Patients:** Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of NovoSeven® RT. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed. **Hypersensitivity Reactions:** NovoSeven® RT should be administered with caution in patients with known hypersensitivity to NovoSeven® RT or any of its components, or in patients with known hypersensitivity to mouse, hamster, or bovine proteins. **Laboratory Tests:** Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin

time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NovoSeven® has been shown to produce the following characteristics: PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7-second plateau at a FVII:C level of approximately 5 U/mL. For FVII:C levels > 5 U/mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following NovoSeven® RT administration is unknown.



INR: NovoSeven® has demonstrated the ability to normalize INR. However, INR values have not been shown to directly predict bleeding outcomes, nor has it been possible to demonstrate the impact of NovoSeven® on bleeding times/volume in models of clinically-induced bleeding in healthy volunteers who had received Warfarin, when laboratory parameters (PT/INR, aPTT, thromboelastogram) have normalized. aPTT: While administration of NovoSeven® shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds. FVIIa:C: FVIIa:C levels were measured two hours after NovoSeven® administration of 35 micrograms/kg and 90 micrograms/kg following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 U/mL for the two dose levels, respectively.

ADVERSE REACTIONS: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice. **Clinical Trials Experience:** Thrombotic events following the administration of NovoSeven® occurred in 0.28% of bleeding episodes treated, with the incidence in acquired hemophilia of 4% and in hemophilia patients of 0.20% in clinical trials within the approved indications [See *Warnings and Precautions*]. Adverse reactions observed in clinical trials for all labeled indications of NovoSeven® included pyrexia, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema, rash (including allergic dermatitis and rash erythematous), pruritus, urticaria, hypersensitivity, cerebral artery occlusion,



NovoSeven® RT
Coagulation Factor VIIa (Recombinant)
Room Temperature Stable

cerebrovascular accident, pulmonary embolism, deep vein thrombosis, angina pectoris, increased levels of fibrin degradation products, disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and AT-III, thrombosis at i.v. site, non-specified thrombosis, thrombophlebitis, superficial thrombophlebitis. The following sections describe the adverse event profile observed during clinical studies for each of the labeled indications. **Hemophilia A or B Patients with Inhibitors:** Two studies (Studies 1 and 2) are described for hemophilia A or B patients with inhibitors treated for bleeding episodes. The table below lists adverse events that were reported in $\geq 2\%$ of the 298 patients with hemophilia A or B with inhibitors that were treated with NovoSeven® for 1,939 bleeding episodes. The events listed are considered to be at least possibly related or of unknown relationship to NovoSeven® administration.

Body System Event	# of episodes reported (n=1,939 treatments)	# of unique patients (n=298 patients)
Body as a whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Hemorrhage NOS	15	8
Fibrinogen plasma decreased	10	5
Skin and Musculoskeletal		
Hemarthrosis	14	8
Cardiovascular		
Hypertension	9	6

Events which were reported in 1% of patients and were considered to be at least possibly or of unknown relationship to NovoSeven® administration were: allergic reaction, arthrosis, bradycardia, coagulation disorder, DIC, edema, fibrinolysis increased, headache, hypotension, injection site reaction, pain, pneumonia, prothrombin decreased, pruritus, purpura, rash, renal function abnormal, therapeutic response decreased, and vomiting. Serious adverse events that were probably or possibly related, or where the relationship to NovoSeven® was not specified, occurred in 14 of the 298 patients (4.7%). Six of the 14 patients died of the following conditions: worsening of chronic renal failure, anesthesia complications during proctoscopy, renal failure complicating a retroperitoneal bleed, ruptured abscess leading to sepsis and DIC, pneumonia, and splenic hematoma and gastrointestinal bleeding. Thrombosis was reported in two of the 298 patients with hemophilia. **Surgery Studies:** Two clinical trials (Studies 3 and 4) were conducted to evaluate the safety and efficacy of NovoSeven® administration during and after surgery in hemophilia A or B patients with inhibitors. In Study 3, six patients experienced serious adverse events: two of these patients had events which were considered probably or possibly related to study medication (acute post-operative hemarthrosis, internal jugular thrombosis). No deaths occurred during the study. In Study 4, seven of 24 patients had serious adverse events (4 for bolus injection, 3 for continuous infusion). There were 4 serious adverse events which were considered

probably or possibly related to NovoSeven® treatment (2 events of decreased therapeutic response in each treatment arm). No deaths occurred during the study period. **Congenital Factor VII Deficiency:** Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that at least 75 patients with Factor VII deficiency had received NovoSeven® - 70 patients for 124 bleeding episodes, surgeries, or prophylaxis regimens; 5 patients in the pharmacokinetics trial. In the compassionate/emergency use programs, 28 adverse events in 13 patients and 10 serious adverse events in 9 patients were reported. Non-serious adverse events in the compassionate/emergency use programs were single events in one patient, except for fever (3 patients), intracranial hemorrhage (3 patients), and pain (2 patients). The most common serious adverse event in the compassionate/emergency programs was serious bleeding in critically ill patients. All nine patients with serious adverse events died. One adverse event (localized phlebitis) was reported in the literature. No adverse events were reported in the pharmacokinetics reports or for the HTRS registry. No thromboembolic complications were reported for the 75 patients included here. As with all therapeutic proteins, there is a potential for immunogenicity. Isolated cases of factor VII deficient patients developing antibodies against factor VII were reported after treatment with NovoSeven®. These patients had previously been treated with human plasma and/or plasma-derived factor VII. In some cases the antibodies showed inhibitory effect *in vitro*. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NovoSeven® RT with the incidence of antibodies to other products may be misleading. **Acquired Hemophilia:** Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven® for 204 bleeding episodes, surgeries and traumatic injuries. Of these 139 patients, 10 experienced 12 serious adverse events that were of possible, probable, or unknown relationship to treatment with NovoSeven®. Thrombotic serious adverse events included cerebral infarction, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Additional serious adverse events included shock and subdural hematoma. Data collected for mortality in the compassionate use programs, the HTRS registry and the publications spanning a 10 year period, was overall 32/139 (23%). Deaths due to hemorrhage were 10, cardiovascular failure 4, neoplasia 4, unknown causes 4, respiratory failure 3, thrombotic events 2, sepsis 2, arrhythmia 2 and trauma 1. **Postmarketing Experience:** The following adverse reactions have been identified during post approval use of NovoSeven®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always

possible to reliably estimate their frequency or establish a causal relationship. The following additional adverse events were reported following the use of NovoSeven® in labeled and unlabeled indications that included individuals with and without coagulopathy: high D-dimer levels and consumptive coagulopathy, thrombosis, thrombophlebitis, arterial thrombosis, and thromboembolic events including myocardial ischemia, myocardial infarction, bowel infarction, cerebral ischemia, cerebral infarction, hepatic artery thrombosis, renal artery thrombosis, intracardiac thrombus, portal vein thrombosis, phlebitis, peripheral ischemia, deep vein thrombosis and related pulmonary embolism, injection site pain and isolated cases of hypersensitivity/allergic reactions including anaphylactic shock, flushing, urticaria, rash, and angioedema [See **Warnings and Precautions**]. Fatal and non-fatal thromboembolic events have been reported with use of NovoSeven® when used for off-label or labeled indications. The Hemophilia and Thrombosis Research Society (HTRS) Registry surveillance program is designed to collect data on the treatment of congenital and acquired bleeding disorders. All prescribers can obtain information regarding contribution of patient data to this program by calling 1-877-362-7355 or at www.novosevensurveillance.com.

OVERDOSAGE: There are no adequate and well controlled studies to support the safety or efficacy of using higher than labeled doses in the indicated populations. Dose limiting toxicities of NovoSeven® RT have not been investigated in clinical trials. The following are examples of accidental overdose. **Congenital Factor VII Deficiency:** A newborn female with congenital factor VII deficiency was administered an overdose of NovoSeven® (single dose: 800 micrograms/kg). Following additional administration of NovoSeven® and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported. A Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 micrograms/kg (10-20 times the recommended dose) and experienced a thrombotic event (occipital stroke). **Hemophilia A or B with Inhibitors:** One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms/kg and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms/kg to 986 micrograms/kg on five consecutive days. There were no reported complications in either case.

More detailed information is available upon request.

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Manufactured by:
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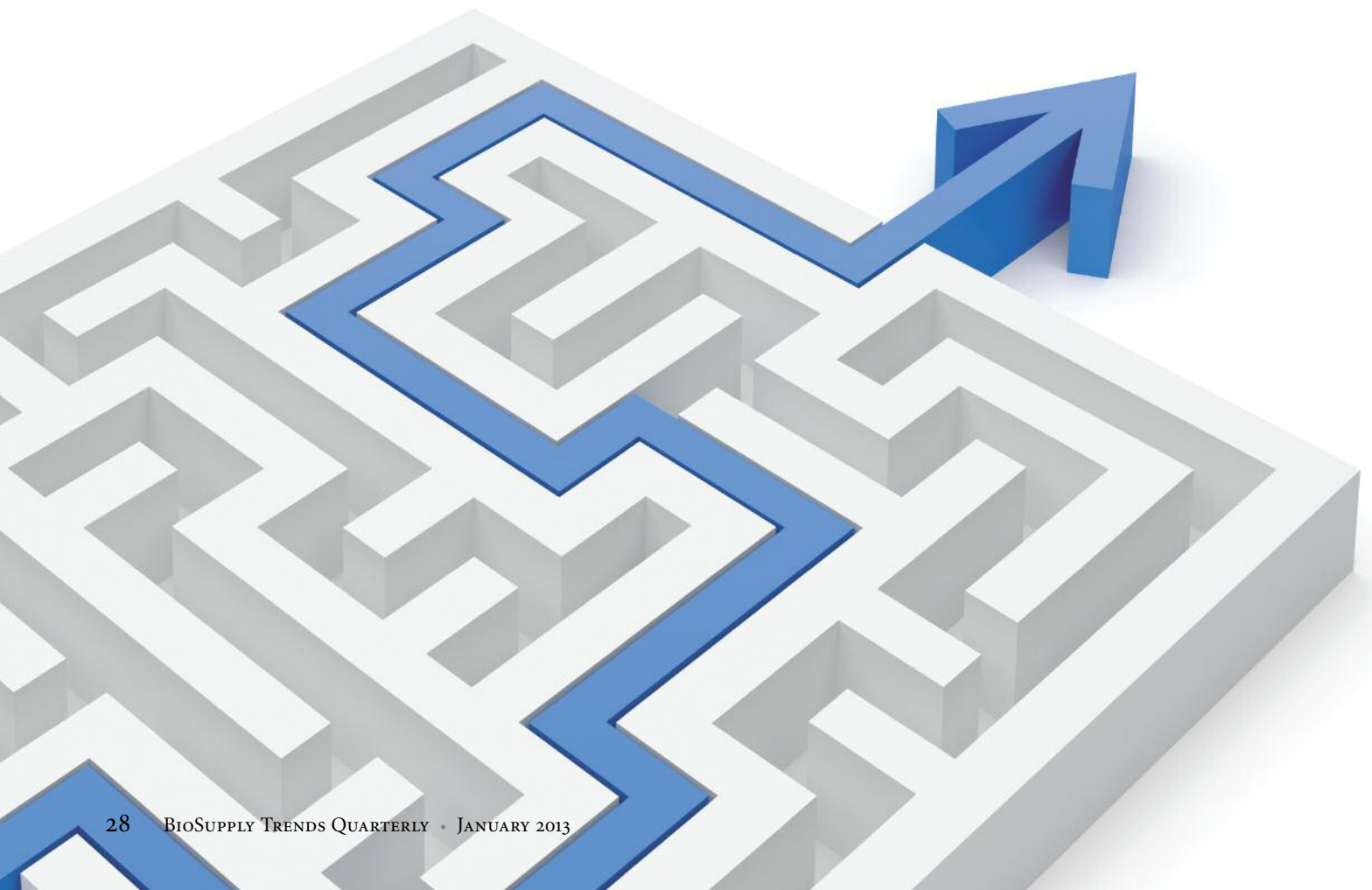
NovoSeven® RT
Coagulation Factor VIIa (Recombinant)
Room Temperature Stable

Immune Globulin:

A Guide to Billing and Reimbursement

Billing for reimbursement of this costly, lifesaving therapy can be complicated, but for the sake of the provider and the patient, getting it right the first time can shorten approval time and prevent denials.

By Ronale Tucker Rhodes, MS, Leslie Vaughan, RPh, and Michelle Greer, RN



Immune globulin (IG) is a U.S. Food and Drug Administration (FDA)-approved therapy to treat primary immunodeficiency diseases (PIDDs), immune-mediated thrombocytopenia (ITP), Kawasaki disease, chronic lymphocytic leukemia (CLL), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN). However, getting reimbursement for the drug can be challenging even for the most experienced providers. What is required when submitting a claim may vary depending on the insurer. Accuracy in submission for authorization is imperative to ensure patients receive therapy when needed and to eliminate the potential for denial by the payer.

Conducting the Benefits Investigation

Prior to initiating IG therapy, the provider who will be administering the therapy should conduct a thorough benefits investigation for the patient. The benefits investigation will reveal whether the payer requires a patient to use a preferred provider, whether pre-authorization is necessary and whether IG therapy falls under the patient's prescription benefit or the major medical benefit. It also will reveal the patient's deductible under the major medical benefit and how much has been satisfied, the maximum patient responsibility and how much has been satisfied, what the plan pays (percentage) and the site-of-care (which may include the patient's home, the physician's office or a hospital outpatient infusion suite) and in-network options. Once the benefits investigation is complete, the provider should notify the patient of his or her options before moving forward with the therapy.

Obtaining Pre-Authorization

Years ago, pre-authorization for IG therapy was not routinely required, but today it is generally required by most commercial payers and by Medicare Part D plans. Once an authorization has been given by a payer, treatment can begin. Typically, pre-authorization is obtained by the provider based on information provided by the prescriber. It is highly recommended to check the payer's requirements for treatment, which usually can be found online or by calling the payer, before applying for authorization.

Prior authorization and insurance coverage for IVIG vary based on the patient diagnosis, where the patient will be infused, who will be submitting claims for the infusion and by the type of payer source. There are many differences between Medicare and commercial insurance. For example, commercial insurance companies typically will reimburse for IG to treat many disease states regardless of whether they are designated as FDA-approved for IG therapy. In the physician office or hospital outpatient setting, IG is reimbursed under Medicare Part B for most diagnosis codes. In the homecare setting, Medicare Part B reimburses for only five specific primary immune deficiency diagnosis codes, which are 279.04, 279.05,

279.06, 279.12 and 279.2. However, Medicare Part D will reimburse for additional diagnosis codes in the home.

The diagnosis codes for the FDA-approved indications other than PIDD listed above are 204.10 (CLL), 287.31 (ITP) 446.1 (Kawasaki disease), 357.81 (CIDP) and 357.9 (unspecified neuropathy) for MMN. Some of the more frequently diagnosed indications that are not FDA approved for IG therapy, but that may be reimbursable include 340 (multiple sclerosis [MS]), 358.00 (myasthenia gravis [MG] without exacerbation), 358.01 (MG with exacerbation), 710.4 (polymyositis), 710.3 (dermatomyositis), 357.0 (Guillain-Barré syndrome [GBS]), 694.4 (pemphigus) and 694.5 (pemphigoid).

Getting reimbursement for IG can be a challenge even for the most experienced providers.

The need to submit the proper ICD-9 code is an important step in the authorization process. An incorrect ICD-9 code may result in a billing error and cause payment delays. The diagnosis code set currently accepted on Medicare claims is ICD-9-CM. While ICD-10-CM codes have been adopted, there is pending legislation to delay implementation of these codes until 2014. Until then, all coding claims must be submitted using an up-to-date ICD-9-CM book. ICD-9-CM codes are valid from Oct. 1 through Sept. 30 of the following year. For example, claims for date of service Oct. 21, 2012, must be coded using valid diagnosis codes from a 2013 ICD-9-CM book.

A very important element of coding is to accurately report a patient's diagnosis, symptom or complaint codes to the highest level of specificity. The ICD-9-CM diagnosis code set includes codes with three, four and five digits. Claims using a three-digit code should be used if there are no four-digit codes within that code's category, and four-digit codes should be used if no five-digit codes exist.¹ For example, claims submitted with ICD-9-CM diagnosis code 279 will be rejected, as more specific diagnosis codes (279.04, 279.05, etc.) are available.

In addition to ICD-9 codes, all diagnoses generally must be substantiated through clinical and diagnostic documentation. This may include office notes and/or a history and physical, lab work, procedures performed during the workup, and any medications tried and failed, not tolerated or contraindicated. Results of any prior response to IG therapy also should be provided if applicable.

Manufacturer Contacts for Billing Assistance

- Baxter BioScience (Gammagard Liquid, Gammagard S/D): www.gammagard.com/healthcare-professionals/ordering-and-reimbursement/billing-instructions.html
- Bio Products Laboratory (Gammaplex): www.gammaplex.com/ordering/coding-billing-information
- CSL Behring (Carimune NF, Hizentra, Privigen): www.cslbehring-us.com/patients-and-families/reimbursement-resource-center/universal-billing-codes.htm
- Grifols (Gamunex-C): www.gamunexconnexions.com
- Kedrion (Gammaked): www.kedrionusa.com/contact.htm
- Grifols (Flebogamma DIF): (888) 474-3657, reimbursementsupport@grifols.com
- Octapharma (Octagam): usreimbursement@octapharma.com

The No. 1 reason for delaying an authorization is incomplete clinical information from the prescriber. Clinical information for PIDD patients should include the history of infections (type, treatment, occurrence), Ig levels (IgG and subclasses, IgM and IgA), vaccination response (failure to show a response to pneumococcal, tetanus and diphtheria vaccines) and other tests depending on the type of immune deficiency.

For neuromuscular diagnoses, results of tests such as a nerve conduction, electromyogram (EMG), muscle biopsy and spinal tap may be required. For example, for CIDP patients, documentation required to approve IG may include EMG, nerve conduction studies, cerebral spinal fluid tests and a history of the symptoms, as well as a complete neurological examination.

Prescribers and providers should be aware of payer requirements to authorize IG therapy. Every payer, whether private or government, has different guidelines for approving IG. Some are very simple, and others are very detailed. If it is determined that the diagnosis is within a payer's guidelines and proof of that diagnosis is submitted, IG should be approved.

Billing for Reimbursement

Billing codes for reimbursement are the responsibility and liability of the provider of IG therapy, including the drug, supplies and nursing costs (if applicable). Codes should include, but are not limited to, national drug codes (NDCs), ICD-9-CM codes and Healthcare Common Procedure Coding System (HCPCS) codes. HCPCS codes are broken into two sets: level 1, which are current procedural terminology (CPT) codes, and level 2, which are J codes.

Each IG product is assigned a unique NDC code that consists of an 11-digit, 3-segment number, which identifies the labeler, product and trade package size. As mentioned previously, the ICD-9-CM codes are those assigned to the indication or

disease state for which the product is being prescribed. CPT and J codes are numbers assigned to every task and service a medical practitioner may provide to a patient, including medical, surgical and diagnostic services. CPT and J codes are used by all payers (although private insurers prefer CPT codes and Medicare favors J codes) to determine the amount of reimbursement that a provider will receive by an insurer. For IG products, the following codes are used: Carimune NF (J1566), Flebogamma 5% and 10% DIF (J1572), Gammagard Liquid (J1569), Gammagard S/D (J1566), Gammaked (J1561), Gammaplex (J1557) Gamunex-C (J1561), Hizentra (J1559), Octagam (J1568) and Privigen (J1459).

Providers bill for the cost of the drug in predetermined increments. For instance, the cost of Hizentra (subcutaneous IG) is billed in 100 mg increments. Therefore, if a patient is receiving 10 grams weekly, the provider would bill for 100 units of J1559 per week. But, Gammaplex (intravenous IG) is billed in 500 mg increments. In this case, for a patient receiving 1,000 mg (equaling 1 gram), the provider would bill for 2 units of J1557. Providers also bill for the costs of supplies and nursing, if applicable. Under Medicare, supplies are billed with one of two codes: K0552: external drug infusion pump, syringe type cartridge, sterile, each or A4221: maintenance of drug infusion catheter, per week. Under private insurance, supplies are billed with S9338: immunomodulating agent — per diem.

For a Medicare patient infusing IG in the home, nursing is reimbursable if the physician certifies the patient is homebound. If a patient is homebound, nursing is 100 percent covered under Medicare Part A when the nursing is provided by a Medicare-certified home health agency. If a patient is not deemed homebound, the cost for a nurse to visit the home may be billed to the patient. For a patient with private insurance, nursing is usually covered with codes 99601: high-tech registered nurse visit (2 hours) and 99602: high-tech registered nurse visit (additional hours).

When billing, providers should be sure to include the authorization number.

How much the provider will be reimbursed for the cost of the drug, supplies and nursing depends upon the contract between the provider and the payer. Medicare sets the reimbursement rates for IG products each quarter, and they are published in each issue of this journal on the BioDashboard page (see page 65), as well as on the Centers for Medicare & Medicaid website at www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html. Medicaid formularies vary by state and can be located on each state's Medicaid site, which can be found at www.medicaid.gov. Private insurers will reimburse the cost of IG therapy based on the provider's contract with the company.

Providers should pay close attention to deadlines for obtaining authorizations and for billing because the duration of author-



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von Willebrand
Factor/Coagulation
Factor VIII Complex
(Human)

I **will** use only high purity VWF/FVIII for my patients with VWD*

I **will** expect reliable dosing and monitoring from a balanced, 1:1 ratio of VWF and FVIII

I **will** demand proven clinical efficacy for acute bleeding in both adult and pediatric patients

I **will** choose the first double virus inactivated VWF/FVIII

*The resulting specific activity of wilate is ≥ 60 IU VWF: RCo and ≥ 60 IU FVIII activities per mg of total protein.

The clinical relevance of this data has not been established

I **will** help my patients take control of VWD

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

For more information, please contact us:

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To report suspected adverse reactions,
Contact Octapharma USA, Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch

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. Patients with VWD, especially type 3 patients, may potentially develop neutralizing antibodies (inhibitors to VWF).

Please see Brief Summary of Prescribing Information, and additional information, on adjacent page.

Print Date 6/12. WIL-004-PAD

octapharma

For the safe and optimal use of human proteins

BRIEF SUMMARY 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.**

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.

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.

- Inform patients that undergoing multiple treatments with Wilate may increase the risk of thrombotic events thereby requiring frequent monitoring of plasma VWF:RCo and FVIII activities.
- Inform patients that there is a potential of developing inhibitors to VWF, leading to an inadequate clinical response. Thus, if the expected VWF activity plasma levels are not attained, or if bleeding is not controlled with an adequate dose or repeated dosing, contact the treating physician.
- Inform patients that despite procedures for screening donors and plasma as well as those for inactivation or removal of infectious agents, the possibility of transmitting infective agents with plasma-derived products cannot be totally excluded.

Manufactured by:

Octapharma Pharmazeutika Produktionsges.m.b.H.
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U.S. License No. 1646

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ization differs from payer to payer. Prior to reauthorization, the payer may require evidence of a positive response to IG, which may be documented in the form of an exam performed by the physician or by lab work.

If deadlines are met and the proper billing procedures are used, providers should be reimbursed without issues. Again, most errors are due to coding mistakes. If there is any doubt or confusion about the proper billing codes, some manufacturers have coding guides or reimbursement staff to assist (see Manufacturer Contacts for Billing Assistance).

Filing an Appeal

There is always a chance authorization may not be granted for IG. When a payer denies authorization of IG therapy, the patient and prescriber will receive a letter stating the denial and the reason. The provider often does not receive the denial letter unless the provider submits the authorization on behalf of the patient.

The No. 1 reason for delaying an authorization is incomplete clinical information from the prescriber.

When a payer denies reimbursement for IG therapy, an appeal can be made. The first thing that should be checked prior to filing an appeal is whether the proper codes were submitted on the claim. If they were correct, an appeal can be made by submitting a letter of medical necessity (LMN) or requesting a peer-to-peer conversation between the prescriber and a medical director from the insurer.

The LMN should state the medical necessity of IG therapy particular to the diagnosis, as well as provide evidence-based medical data that pertain to the physician's diagnosis. A search of medical journals will turn up studies that substantiate the effectiveness of IG therapy for a particular disease state. In addition, the LMN should indicate the failure or intolerance of other therapies. A prior response to IG therapy should be included. Instructions on how to appeal are always included in the denial letter.

In some cases, rather than a written appeal, a conversation known as a peer-to-peer may be better, especially for complex cases. In this situation, the prescribing physician and the insurance company's medical director can discuss the justification

for IG therapy. The denial letter provides instructions for requesting a peer-to-peer review.

It's important to note that under the Affordable Care Act, there are new health insurance appeal rules that apply to health plans created or purchased after March 23, 2010.² Specifically, when a payer denies payment for a treatment or service, the patient can request an appeal, and the payer is required to review its decision. For plan years or policy years beginning on or after July 1, 2011, when the payer denies a claim, it must notify the patient of the reason the claim was denied, the patient's right to file an internal appeal, the right to request an external review if the internal appeal is unsuccessful, and the availability of a consumer assistance program (if the state in which the patient resides has one).

When an internal appeal is filed, the payer must give a decision within 72 hours after receiving the request when appealing the denial of a claim for urgent care, within 30 days for denials of non-urgent care not yet received, or within 60 days for denials of services already received. If after an internal appeal the payer still denies the request for payment or services, the patient can ask for an independent external review by an organization that will decide whether to uphold or overturn the payer's decision. If the external review organization overturns the payer's denial, the payer must reimburse the claim.

The internal appeals rights under the Act take effect when the plan starts a new plan year or policy year on or after Sept. 23, 2010. The external review rights took effect Jan. 1, 2012 (although some states already have an external review process that meets the new rules).

Accuracy and Timing Are Crucial

Patients who rely on IG therapy could be placed at great risk of medical complications should they be denied coverage. With the prohibitively high cost of IG therapy, most patients are unable to afford the drug without coverage. What's more, when an appeal is necessary, patients, physicians and infusion providers all face financial hardship with time-consuming delays in the appeals process. Therefore, accurate and thorough authorization and error-free billing practices will provide a win-win situation for all when this critical lifesaving therapy is needed. ❖

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Research Developments for Multiple Sclerosis

By Amy Scanlin, MS

Advances in research are showing promise for new treatments for this chronic and disabling disease.

The challenge concerning multiple sclerosis (MS) is not just understanding its cause. It also includes diagnosing the disease and understanding its progression and how patients respond to treatment.

MS is a chronic and often disabling disease that attacks the central nervous system, which is made up of the brain, spinal cord and optic nerves. Symptoms may be mild, such as numbness in the limbs, or severe, such as paralysis or loss of vision. The progress, severity and specific symptoms of MS are unpredictable and vary from one person to another.¹

MS can be diagnosed only after ruling out other conditions. This is because MS often presents with symptoms that are similar to other diseases. Yet, despite the fact that diagnostic criteria for diagnosing MS were updated in 2010, and guidance on how to discern MS from other look-alike disorders was updated in 2008, the misdiagnosis of patients who are later found to not have the disease is still far too high. And, the costs of treating these misdiagnosed patients is estimated to surpass \$11 million annually for medical treatment alone, or about \$40,000 per patient.²

Reasons for misdiagnosis are due to symptoms that mimic those of other nervous system disorders and, potentially, to the overreliance on MRIs. Diagnoses left to physicians who are not neurologists specializing in the disease often pose a real risk of misdiagnosis.³ In fact, a survey of MS specialists found that 95 percent have consulted with at least one patient who was incorrectly diagnosed, and 40 percent of specialists have seen three to five misdiagnosed patients in the last year. It is estimated that about 10 percent of patients who have been diagnosed with MS have some other disease⁴ that is later found to be a nonspecific brain abnormality, tumor-like lesion, small blood vessel ischemic disease, migraine, neuromyelitis optica or something else.

“The impetus now,” says Dr. Nick LaRocca, vice president of healthcare delivery and policy research at the National Multiple Sclerosis Society, “is to go back and re-examine the phenotype classification because it has important implications for not just establishing diagnosis, but also for classification of patients. There is an increasing interest in looking at patients prior to the point where they had their first event.” For instance, physicians are looking at a patient’s first demyelinating event, when a diagnosis could not yet be pinpointed, at which time the possibility of treatment could have been discussed with the patient. “When symptoms seem to suggest MS,” says Dr. LaRocca, “there is a dialogue between patient and physician to determine if they should go forward with treatment or wait to see what transpires.” Dr. LaRocca says the field has been moving in the area of earlier treatment because literature shows it helps prevent the compounding of symptoms. “There is the possibility of losing ground you can’t make up,” he says.

Today, new treatments and advances in research are giving new hope to people affected by the disease.

Interferon Beta

Fine-tuning a patient’s immune response to MS is one area of research showing promise in improving patient outcomes.

Anti-viral proteins such as interferon beta protein drugs are being tested in more than a dozen clinical trials as a method for reducing exacerbations and possibly slowing the progression of physical disability caused by the relapsing-remitting form of MS, as well as shortening the length and severity of attacks. Three U.S. Food and Drug Administration-approved drugs for treatment of relapsing-remitting MS in the beta interferon category are Avonex, Betaseron and Rebif.⁵

Today, new treatments and advances in research are giving new hope to people affected by the disease.

An observational study supported by the National Multiple Sclerosis Society and recently published in *JAMA* showed that interferon beta drugs (which are controversial as to the extent they slow disease progression) may not actually slow progression at all. The study was somewhat limited in that it viewed only treated versus untreated patients; it was not a randomized placebo-controlled trial, and the study authors themselves suggest that the debate will continue.⁶ The authors even list in their accompanying commentary a novel study showing that disease-modifying drugs (DMDs) do demonstrate a significant reduction in progression.⁷

Whether DMDs are found to slow progression or not, there is no question that this first-line therapy shows positive effects on relapse reduction and lesion outcomes.⁸

T Cell Suppression

Daclizumab (Zenapax), a monoclonal antibody and a key factor in indirectly suppressing T cell response in interleukin-2, has been shown in large-scale studies to be effective as an add-on therapy to interferon beta. It is now also being tested to see if it could be an effective stand-alone therapy as well.

Indeed, one study of daclizumab as a stand-alone therapy has shown a positive effect of daclizumab on stimulation of killer T cells and inhibition of lymphoid tissue inducer (LTi) cells. (This study is a first implicating LTi cells in an autoimmune disorder.) Patients taking the drug had reduced inflammation of cerebrospinal fluid (CSF) and a reduction of stem cell devel-

opment into an LT_i cell in favor of a natural killer cell (which explains why natural killer cells are expanded in patients taking daclizumab therapy).⁹

Also interesting in the study was the fact that the IgG index was reduced in patients taking the drug for six-and-a-half months as measured by inflammation of the CSF, though thus far the link is indirect. Researchers reasoned that LT_i's cell suppression should reduce growth of abnormal lymphoid follicles, which are believed to lead to chronic brain inflammation in those with MS. The CXCL-13 protein linked to lymphoid growth was decreased by approximately 50 percent, and the IgG index indicating antibody production decreased by more than 13 percent. If further research supports the findings that these cells play an important role in MS, the development of therapies that selectively inhibit LT_i formation could be a useful therapy.⁹

B Cell Toxicity

Researchers are taking a close look at B cells, which are more active in the blood and brain of those with MS, and the possibility that these cells may produce toxic factors that harm brain cells, in particular those that make myelin. It appears that B cells may secrete a substance that is toxic to oligodendrocytes and either directly or indirectly impact myelin-making cells.

The study of biomarkers in MS patients is another exciting area of research, and nearly all major MS drugs have a biomarker-related study ongoing.

Though the evidence has not been confirmed, research trials of the cancer drug rituximab (Rituxan and MabThera) are looking at how the drug targets B cells and reduces MS relapses and brain lesions via a “genetically engineered chimeric monoclonal antibody that depletes CD20+ B cells through a combination of cell-mediated and complement-dependent cytotoxic effects and the promotion of apoptosis.”¹⁰ The drug is showing promise, though it has some side effects. Identifying the toxic substance(s) produced by B cells can serve as a new path for development of treatment therapies.¹¹

During a 48-week study, patients taking rituximab saw a significant reduction in the number of gadolinium-enhancing

lesions and the number of relapses after just four weeks (the first dose), though the predominant mechanism for this is unknown. Because rituximab does not target plasma cells, it is thought that the outcome could be due to “lysis of memory B cells located in the peripheral blood and lymphoid tissues, or perhaps in the central nervous system. Interference with antigen presentation by B cells, or with activation of T cells or macrophages by pro-inflammatory B-cell cytokines such as interferon- γ and interleukin-12, may also play a role.” Patients who concluded the 48-week study overall saw a “rapid and complete depletion of CD20+ peripheral B cells (as measured by CD19 expression).”¹⁰ While this short study was not designed to assess safety of the drug, it shows promise in the potential for rituximab.

Another therapy currently in a Phase III study is ocrelizumab, an “investigational, humanized monoclonal antibody designed to selectively target CD20-positive B cells” and then interact with the body’s immune system to eliminate them.¹² These B cells appear to trigger a T cell attack on the nerve fibers of the brain, so by blocking the B cells, a T cell attack could be stopped.

The Phase II study of ocrelizumab showed the drug allowed patients to maintain a significant decrease in disease activity for nearly two years in those with the relapsing-remitting form of MS. During the study period, no patient who received a dose of 600 mg ocrelizumab developed a new or enlarging brain lesion (as measured by MRI), and two-thirds of those patients who completed the study were free of disease activity (as measured by MRI, relapses or neurological progression). Only 6 percent of the study participants taking ocrelizumab showed adverse effects.¹³ Patients with the primary-progressive form of MS have been included as part of the ocrelizumab Phase III study.¹²

Biomarkers

The study of biomarkers in MS patients is another exciting area of research, and nearly all major MS drugs have a biomarker-related study ongoing. However, at this point, it is yet unknown what the exact immune response of MS is. “There is a tremendous amount of interest in this,” says Dr. LaRocca, “because MS is so complex and varies so much from person to person. For instance, vision loss is a major problem for some, but for others vision is OK but they can’t walk. For others, it is cognitive. So, what do you pick as your criteria when looking at progression? At this point, we don’t know what that is.”

The present “sledgehammer” versus “scalpel” approach, as National Multiple Sclerosis Society blogger Julie Stachowiak, PhD, puts it, uses drugs that delete parts of the immune system and leave patients vulnerable to other diseases. Yet, there are a few new biomarker findings that show

promise for the future of MS patients.¹⁴ The anti-JCV antibody test for those taking Tysabri (natalizumab injection) indicates whether there is a risk of progressive multifocal leukoencephalopathy (PML), a rare and usually fatal viral disease characterized by progressive damage or inflammation of the white matter of the brain at multiple locations. Those testing positive have a one-in-100 chance of PML, and those who test negative have just a minuscule chance. Also, interleukin-17 (IL-17) testing for suboptimal responders of interferon beta drugs indicates that those with very high levels of IL-17 (about 10 percent of those with MS) won't respond to this therapy.

“The researchers who have dedicated their lives to this study should be congratulated as they are trying to accomplish a world free of MS.”

Other research in the area of biomarkers has not yielded equally successful results. For example, anti-myelin antibodies, analysis of microarray gene expression, and studies of CSF have not yielded specific and sensitive biomarkers for either the disease itself or the prediction for development. However, serum biomarkers monitoring therapeutic efficacy such as the titer of antibody to beta interferon already are used clinically.¹⁵

Much effort in biomarker research revolves around the monitoring of disease activity. At present, a disease “activation” panel of CSF biomarkers includes interleukin-6 or its soluble receptor, nitric oxide and nitric oxide synthase, osteopontin and fetuin-A.¹⁶

A recently published large-scale study in the journal *Nature* identified 29 new genetic variants and confirmed 23 others associated with MS. Most of these genes are related to immune function, and one-third have previously been identified for association with other autoimmune diseases. Many as well were associated with T cell function and proliferation.¹⁶

“In the next few years, we may see an ideal biomarker,” says Dr. LaRocca. “We’ll test a lot of things and find out what works and what doesn’t. That’s one reason negative studies are so important.” In the meantime, the complex causality of MS is both good news and bad. The bad news is that it’s harder to

treat. But, says LaRocca, “maybe we can address factors that turn out to be easy. The more we know, the closer we will be.”

The Way Ahead

“We are fortunate that so many therapies are available and in the pipeline,” says Dr. LaRocca about the future for MS research and patient care. “Most importantly, we really want to see to it that those who have MS are able to live well with their disease. That’s the goal of the National Multiple Sclerosis Society, other MS organizations, physicians and researchers. We are keeping the focus on the person and working in a way that maximally benefits those with MS. The researchers who have dedicated their lives to this study should be congratulated as they are trying to accomplish a world free of MS.” ❖

AMY SCANLIN, MS, is a freelance writer and editor specializing in medical and fitness topics.

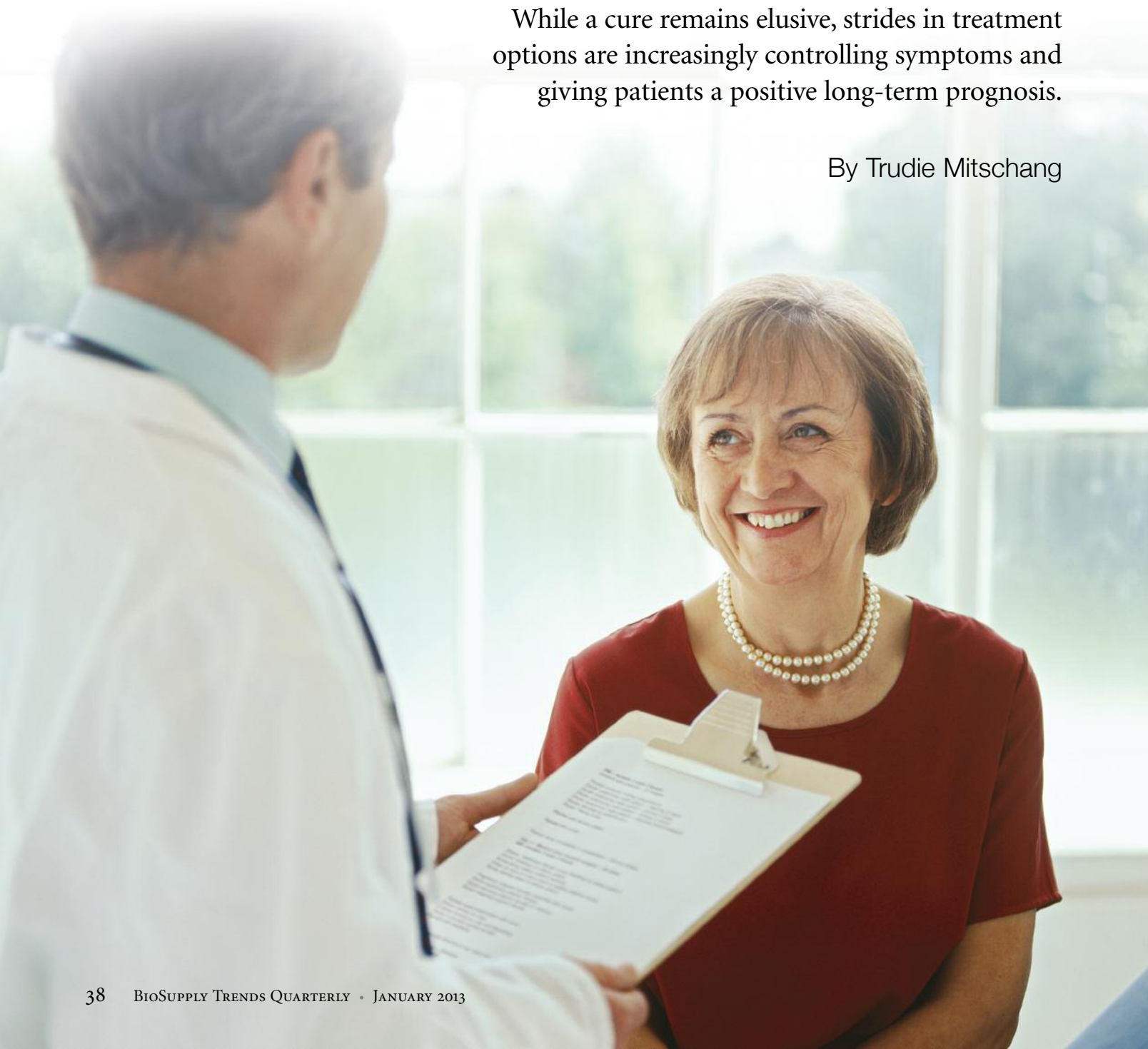
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Cancer: The New Chronic Illness

While a cure remains elusive, strides in treatment options are increasingly controlling symptoms and giving patients a positive long-term prognosis.

By Trudie Mitschang



The word “cancer” used to be uttered in hushed tones, as if naming the disease aloud was in itself contagious. Once considered an automatic death sentence with a post-diagnosis life expectancy that could be calculated in months if not weeks, today cancer is a disease that millions of people are living with long-term. Thanks to improved traditional and alternative treatment options, advanced research targeting specific types of cancer, and access to better medical care, the outlook for many types of malignancies is often cautiously optimistic.

There are many reasons for the paradigm shift concerning expected cancer outcomes, including improved symptom control and less toxic therapies. In addition, more clinical trials for experimental therapies are available today than ever before, offering patients with metastatic cancer varied options when it comes to disease control, even after standard treatment options have failed.

Many cancer patients for which only a single therapy was available just a few years ago now have second- or even third-line therapies at their disposal. Patients are able to live longer by using one therapy for a period of time, and when effectiveness wanes, they simply move on to a different option. This model of care has been dubbed the “hitchhiker model” to describe patients who jump from therapy to therapy. The longer patients survive, the greater their chances of plugging into a promising clinical trial or going into remission.

“Cancer treatment today is less likely to follow the traditional model of offering one or two lines of systemic cancer treatments and then focusing on end-of-life care, but patients often still think that way,” says Michael Fisch, MD, associate professor of gastrointestinal medical oncology and director of the MD Anderson General Oncology Program. “The goal of therapy is often turning out to be one of maximizing the area under the quality-of-life-over-time curve — extending life and maintaining quality of life as long as possible and by whatever means are available in patients who cannot be cured.”¹

Understanding Cancer

According to the American Cancer Society, cancer is the second leading cause of death in the United States.² To put that in perspective, about one-half of all men and one-third of all women in the U.S. will develop cancer during their lifetimes. There are literally millions of people who are living with cancer or have had cancer.

Cancer is an incurable disease that can be closely watched and even treated, but in many instances, it never completely goes away. When this happens, it becomes more of a chronic illness much like diabetes or heart disease. This is often the case with certain cancer types, such as ovarian cancer, chronic leukemias and some lymphomas. Sometimes cancers that have spread or have come back in other parts of the body, like

metastatic breast or prostate cancer, also become chronic cancers. Some of the attributes of a “chronic” cancer include:

- the cancer is controllable with treatment;
- the cancer does not grow or spread as long as treatments are maintained;
- treatment shrinks the cancer, allowing patients to take a break from treatment and simply monitor the situation, resuming treatment if the cancer reappears.

In these scenarios, the cancer is not cured; rather, it has become temporarily asymptomatic. A clinician may use the term “controlled” if tests or scans show that the cancer has stabilized over time.

Many cancer patients for which only a single therapy was available just a few years ago now have second- or even third-line therapies at their disposal.

Targeting Therapies for Cancer

Many people are willing to try a variety of treatments when battling cancer. Treatment decisions are based on the type of cancer, location of the cancer, amount of cancer, extent of spread, the patient’s age and overall health, and, of course, the patient’s personal preferences. When devising a treatment plan, for example, a physician would typically not suggest radiation or surgery for cancer that has spread throughout the body, while this type of treatment could be effective for isolated tumors that are caught in their early stages.

In recent years, treatment options for cancer have expanded due to increased knowledge regarding the disease’s molecular roots. Researchers have successfully identified abnormal proteins that promote cancer proliferation, which has led to the development of agents that block those proteins or induce their normal expression. These agents are known as target therapies because they interfere with specific molecular pathways to cancer, in contrast to older, broadly cytotoxic chemotherapies. Since target therapies are generally less harmful to patients and can be administered for greater lengths of time compared with traditional chemotherapies, targeted therapies are emerging as a crucial component of cancer management.¹

One of the first agents developed to target a specific molecular



pathway (the tyrosine kinase inhibitor, imatinib [Gleevec]) has dramatically reduced disease progression rates for patients with chronic myelogenous leukemia (CML).¹ Although imatinib resistance sometimes develops, those patients are often able to turn to next-line therapies for CML, using therapies that didn't even exist a decade ago.

Promising results also are being seen with targeted therapies used to treat solid tumors such as renal cell carcinoma. Until 2005, the only agents available for metastatic conventional-type renal cell carcinoma were the cytokines interferon and interleukin-2. About 5 percent of patients could be cured with high-dose, bolus interleukin-2 and only 1 to 2 percent with interferon; these therapies were highly toxic and suitable only for young patients with no brain metastasis. Thankfully, during the period from 2005 to 2007, three new agents were

approved: sorafenib (Nexavar), sunitinib (Sutent) and temsirolimus (Torisel). In one large-scale Phase II clinical trial, temsirolimus was associated with an increase in median survival rate of nearly 50 percent for patients with advanced renal cell cancer.³

"We're not curing these patients, but they are living longer," says Dr. Nizar Tannir, associate professor in the Department of Genitourinary Medical Oncology of the MD Anderson General Oncology Program. "I think it's fair to say that these drugs have changed the landscape of renal cell cancer. Renal cell cancer has pulled away from the pack of those dreaded cancers where, for metastatic disease, there has not been any meaningfully effective therapy."¹

In recent years, treatment options for cancer have expanded due to increased knowledge regarding the disease's molecular roots.

In addition to these newer therapies, other agents are currently in the pipeline, giving oncologists the opportunity to offer patients multiple lines of therapy that can ultimately help them live longer. As genetic profiling improves, clinicians may be able to identify those who could benefit from experimental therapeutics before they undergo cytotoxic chemotherapy. This is helpful since chemotherapy often makes patients ineligible for new agent trials.

The Self-Care Component

Years ago, patients diagnosed with cancer required regular hospital visits in order to receive chemotherapy either intravenously or through injection. Now, many chemotherapy regimens can be delivered in pill form, allowing patients to administer the drug themselves. This is helpful for patients looking at long-term cancer management; however, it does require patients to take greater responsibility for their disease management. Obviously, success is determined by their willingness to adhere carefully to their treatment plan and take prescribed medications properly.

Ethan Basch, MD, medical oncologist and health services researcher at Memorial Sloan-Kettering Cancer Center in New York, who has expertise in patient-reported outcomes, clinical

informatics and drug regulatory policy, says it is vital for patients with cancer to fill prescriptions and take medication as directed, and he explains the implications for not doing so: “Many medications are prescribed based on studies evaluating benefits and risks at specific doses and schedules of administration. Therefore, if these medications are not taken as directed, they may not yield the expected effects.”

The most common reason for patient noncompliance during self-administered cancer treatment is the onset of adverse side effects. “If a patient is experiencing side effects possibly related to a medication, the best approach is to start by discussing this with the prescribing clinician to assess possible causes and to consider changes in the dose or schedule based on best practices, or to consider alternative treatments,” says Dr. Basch.⁴

Other challenges patients utilizing the self-care model may face include cost, inconvenience, confusing dosing schedules (for example, treatments that require intermittent dosing) and simply forgetting to take medication.

The Treatment Timeline

Patients with a cancer diagnosis and long-term treatment plan often wonder how long they will need to continue treatment. Because of the unpredictable nature of cancer, this can be a difficult question to answer. The answer depends on the specifics of each patient’s situation and many influencing factors, including:

- type of cancer
- treatment method
- length of time between cancer recurrences
- aggressiveness of the cancer cell type
- patient’s age
- patient’s overall health status
- level of treatment tolerance
- how well the cancer responds to treatment
- types of treatment available

Chronic cancers cannot be cured, but some can be controlled for months or even years. In some cases, there also is the possibility that the cancer will go into remission. There are two types of cancer remissions: 1) when a treatment completely gets rid of all tumors that could be measured or seen on a test. This is referred to as a complete response or complete remission. And, 2) a partial response or partial remission, which means the cancer partly responded to treatment, but still did not go away. A partial response is most often defined as at least a 50 percent reduction in measurable tumor.

To qualify as either type of remission, the reduction in the size of the tumor must last for at least one month. Because it is impossible to predict how long a remission will last, neither type of remission implies the cancer has been cured.

Some cancers such as ovarian have a natural tendency of recurrence and remission. Often, this repeating cycle of

growing, shrinking and stabilizing can mean survival for many years, during which the cancer can be managed as a chronic illness.⁵ In these instances, treatment can be used to control the cancer, help relieve symptoms and allow patients to live longer.

The Psychological Impact

Because there are no guarantees with cancer treatment, chronic cancer can be difficult to cope with, even when symptoms seem to be manageable. Patients are encouraged to maintain open lines of communication with their physicians. It also is helpful to remind patients living with cancer that as with any chronic disease, it is not so much about “getting back to normal” as it is learning what is normal now. For many people, a cancer diagnosis will require long-term dietary changes and lifestyle adjustments. Simply fitting cancer treatments into a work or vacation schedule can add stress to an already overwhelming situation. For many, it can mean making treatment part of everyday life.

*Chronic cancers cannot be cured,
but some can be controlled
for months or even years.*

While finding a cure for cancer remains the ultimate medical research goal, the chances for long-term cancer control hold significant promise for cancer patients today. As more is learned about the genetic profiles of specific cancers, access to effective cancer management will only increase, extending lifespan and improving quality of life for patients diagnosed with all types of this relentless disease. ❖

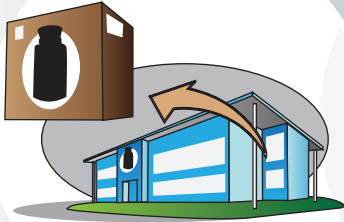
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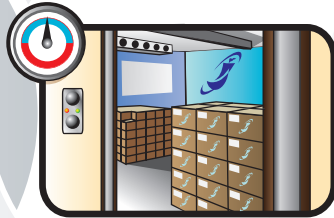
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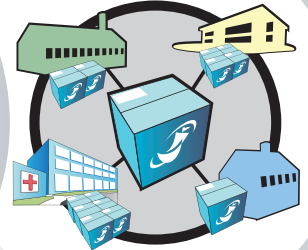
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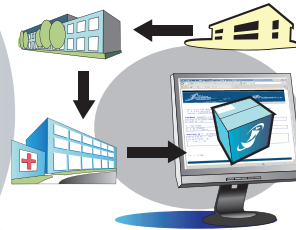
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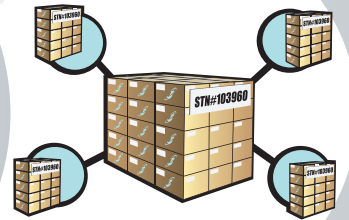
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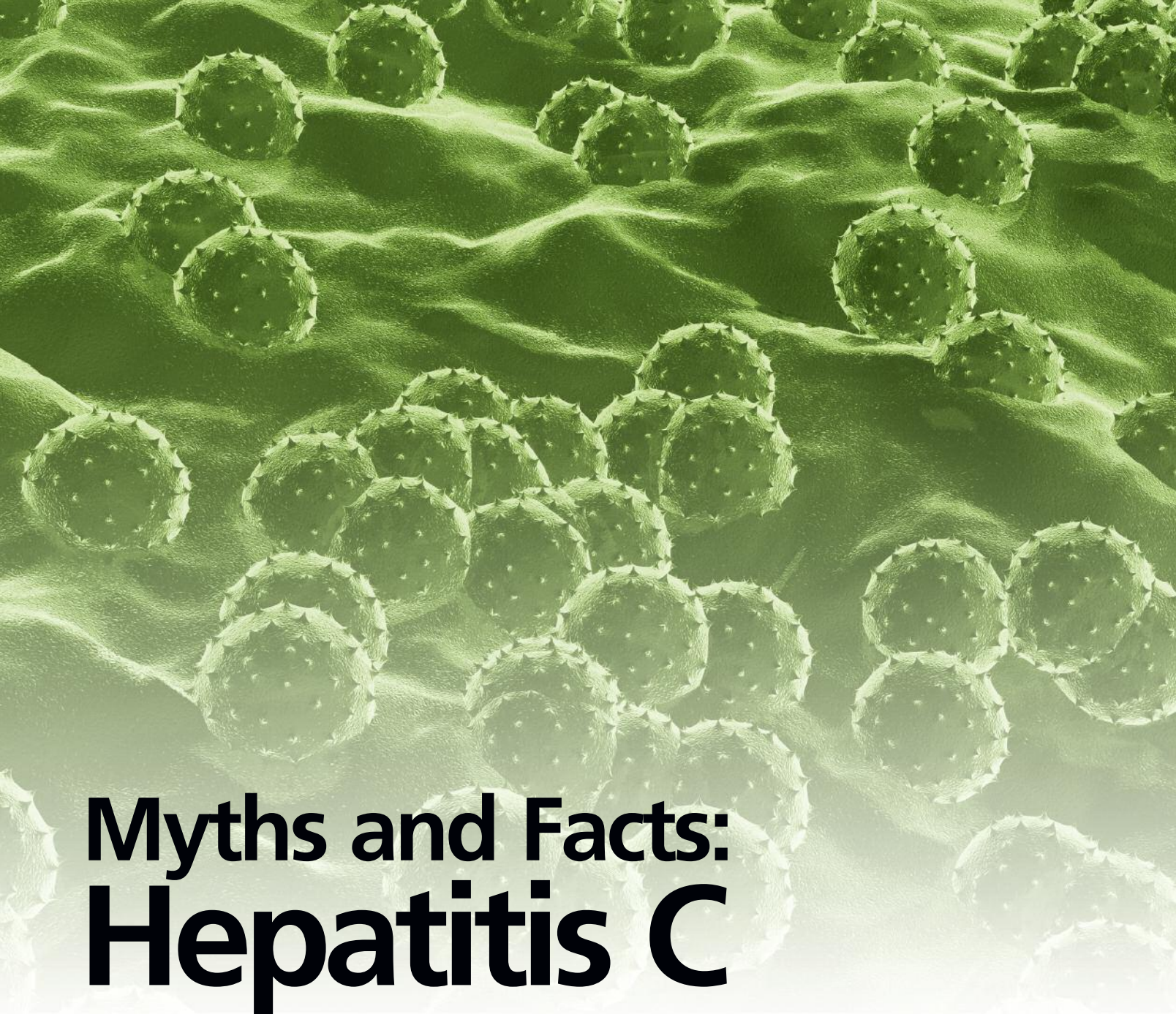
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Myths and Facts: Hepatitis C

By Ronale Tucker Rhodes, MS

The hepatitis C virus affects 130 million to 170 million people worldwide, and the numbers are growing. But with a better understanding of the disease and advances in treatment, it no longer has to be a death sentence for most.

Last August, the Centers for Disease Control and Prevention (CDC) issued a public recommendation that U.S. resident baby boomers born between 1945 and 1965 be tested for the hepatitis C virus (HCV).¹ HCV is a contagious disease that is caused by a virus that infects the liver. It is only one of five types of hepatitis that is spread when a person is exposed to the blood of another person who has the virus.

The CDC recommendation was in response to a recent study published in the *Annals of Internal Medicine* that found HCV causes 15,000 deaths annually, and that number is rising.² Baby boomers make up more than two million of the 3.9 million U.S. residents who have HCV. Since most individuals with HCV have no symptoms, and the infection often leads to cirrhosis and liver cancer, the CDC's strategy for baby boomers to receive a one-time, voluntary test for the virus is to identify a potential 800,000 new cases and to prevent potentially 120,000 deaths.

HCV was only identified in 1989, but the medical profession has come a long way in understanding the disease. Unfortunately, the increasing health burden and mortality from HCV in the U.S. are significant. By 2007, HCV had superseded HIV as a cause of death in the U.S.¹ And, while deaths from HCV have disproportionately occurred in middle-aged persons, all ages are at risk. Therefore, understanding the facts about this disease is becoming increasingly more important.

Separating Myth from Fact

MYTH: HCV is not a prevalent disease.

FACT: The prevalence of HCV is increasing worldwide. According to the World Health Organization, approximately 130 million to 170 million people are chronically infected with HCV, and more than 350,000 people die from HCV-related liver disease each year. In the U.S., the CDC estimates that 1.8 percent, or 3.9 million, Americans have been infected with HCV, 2.7 million of whom are chronically infected.³

MYTH: HCV is not a serious disease.

FACT: HCV is a potentially lethal disease. In 15 percent of cases, people experience acute HCV, which means it lasts less than six months, and symptoms are generally mild and vague, including a decreased appetite, fatigue, nausea, muscle or joint pain, and weight loss. In the other 85 percent of cases, HCV infection is chronic. Most people with chronic HCV experience minimal or no symptoms during the initial few decades of the infection. If left undiagnosed and untreated for many years, chronic HCV becomes the primary cause of cirrhosis and liver cancer. In fact, about 10 percent to 30 percent of people develop cirrhosis over 30 years. Those who develop cirrhosis have a 20-fold greater risk of hepatocellular carcinoma, and for those who drink alcohol in excess, the risk becomes 100-fold greater. Chronic HCV is the cause of 27 percent of

cirrhosis cases and 25 percent of hepatocellular carcinoma worldwide. It also is the most common reason for liver transplantation in the U.S.⁴

MYTH: People with HCV would know if they have the disease.

FACT: In the U.S., 80 percent of people who have chronic HCV don't know it. The reason is that they don't look or feel sick even though the virus may be causing damage to their liver. Indeed, most people with chronic HCV don't have symptoms until serious liver damage develops. In addition, 70 percent of people with chronic HCV don't know how they got it. Therefore, if someone has any reason to believe HCV has been contracted, he or she should be tested for it.⁵

*HCV was only identified
in 1989, but the medical
profession has come a long
way in understanding
the disease.*

The CDC recommends screening for HCV infections in the following persons: those having ever injected illegal drugs; those having received a blood transfusion or organ transplant before July 1992 (when the blood supply began being monitored in the U.S.); those having received clotting factor concentrates produced before 1987; those ever on long-term dialysis; children born to HCV-positive women; healthcare, emergency medicine and public safety workers after needlesticks, sharps or mucosal exposure to HCV-positive blood; and those with evidence of chronic liver disease.⁶

MYTH: Hepatitis A can lead to hepatitis B, which can then lead to HCV.

FACT: There are five types of hepatitis viruses — A, B, C, D and E — each of which differs in structure, exposure and disease. If a person had hepatitis A and now has HCV, that person was infected with two different viruses; one virus can't change into another. The only thing the viruses have in common is that they all affect the liver.⁷

MYTH: Most people have been vaccinated against HCV.

FACT: A vaccine to prevent HCV is often confused with one for hepatitis A or B. While there is an approved vaccine for use in the U.S. for hepatitis A and B, there is not one for HCV. Researchers are experiencing breakthroughs in HCV vaccine development; however, creating an effective vaccine is proving

difficult since the virus constantly mutates.⁸

MYTH: All people infected with HCV have the same virus.

FACT: Not all types of HCV are the same. There are at least six major distinct strains, or genotypes, numbered one to six in order of discovery, and 50 variants or subtypes within genotypes designated by letters as 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4a, 5a and 6a, etc. These different genotypes are a result of mutations when the virus replicates.

In the U.S., genotype 1 (subtypes a and b) is the most common, accounting for 83 percent of HCV cases. People infected with genotype 1a or 1b have a more severe type of HCV, are less likely to respond to treatment than genotypes 2 or 3 and usually require longer therapy. Those with genotype 1b are significantly older than patients with other genotypes because they were infected in the 1960s when drug experimentation was predominant. Genotype 2, a milder form of HCV, accounts for 12 percent of U.S. cases. And, genotype 3 accounts for 5 percent of U.S. HCV cases. This genotype has been linked to fatty liver due to an enzyme known to play a crucial role in lipid production that has been found at high levels in human liver cells exposed to HCV.⁹

The possibility of becoming infected with more than one genotype, known as superinfection, is possible if risk factors for HCV infection continue. Superinfection happens when a cell previously infected by one virus becomes co-infected with a different strain of the virus. Studies have shown that HCV reinfection and superinfection are common among actively injecting drug users. And, in rare cases, a sexually transmitted HCV superinfection in HIV/HCV co-infected patients with high-risk sexual behavior have been reported.¹⁰

In the U.S., 80 percent of people who have chronic HCV don't know it.

MYTH: HCV is a sexually transmitted disease (STD).

FACT: While there is some truth to this, HCV is a disease of the liver that is spread through blood-to-blood exposure. HCV can be transmitted sexually, but the risk is very low in most populations. The majority of studies have shown a 0 percent to 3 percent prevalence in HCV in people in stable, monogamous heterosexual relationships. For those in high-risk groups, however, usually defined as people with multiple sexual partners, men who have sex with men, women who have sex with women, prostitutes and people seen at STD clinics, the

risk of contracting HCV through unsafe sex is believed to be higher, although more studies are needed.⁸

MYTH: People with HCV are alcoholics and/or drug users.

FACT: While many people with HCV are alcoholics, and half of all new cases of HCV are drug users, it is untrue to say that all people with HCV are alcoholics and/or drug users. That would be the same as saying all diabetics are overweight.

There is a different type of hepatitis called alcoholic hepatitis that is linked with alcohol, but someone who drinks alcohol in moderation might develop alcoholic hepatitis, while very few people who drink excessive amounts of alcohol develop alcoholic hepatitis. The only similarity between HCV and alcoholic hepatitis is that they both often lead to cirrhosis, which could lead to liver failure.⁷

MYTH: HCV viral load correlates to symptoms and disease progression.

FACT: The HCV viral load is the number of viral particles, or copies of the genetic material of the virus, floating in the blood (circulating through the body). Viral load is based on technology that measures extremely small quantities of HCV RNA, the building block of the virus.¹¹ Viral load is measured to confirm active infection, to predict treatment response, to make sure HCV medications are working during treatment, and to make sure the virus is still undetectable after treatment is completed.⁸

No studies have shown that someone with a higher viral load has more symptoms compared with someone with a lower viral load. And, while it's logical to assume that if a person has more virus (a higher viral load), they would experience a faster disease progression, but studies have not shown a correlation between the amount of the virus and the degree of liver damage.⁸

MYTH: Liver enzyme levels are a predictor of HCV disease progression.

FACT: Many experts don't believe that measurement of liver enzymes is a good predictor of HCV progression. Instead, they submit that the only way to really tell whether HCV has progressed to the point of liver damage is by doing a liver biopsy. Liver enzyme levels are measured through alanine aminotransferase (ALT), an enzyme that is produced in liver cells and released into the bloodstream when there is damage taking place in the liver. While most people with HCV and normal ALT levels have minimal liver disease progression, about 20 percent with normal ALT levels have moderate to severe HCV disease progression.⁸

MYTH: People with chronic HCV shouldn't take Tylenol.

FACT: Doctors often recommend acetaminophen (Tylenol) to relieve symptoms associated with HCV and treatment-related side effects. In fact, clinical data demonstrate that acetaminophen is an appropriate pain-relief choice for patients with chronic liver disease. According to a literature review,



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About AFLURIA

AFLURIA is an inactivated influenza virus vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. AFLURIA is approved for use in persons 5 years of age and older.

Select Safety Information

AFLURIA is contraindicated in individuals with known severe allergic reactions (eg, anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine.

Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with postmarketing reports of increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years; these increased rates were confirmed by postmarketing studies. Febrile events were also observed in children 5 to less than 9 years of age.

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

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

Antibody responses in persons 65 years of age and older were lower after administration of AFLURIA as compared to younger adult subjects.

In children 5 through 17 years of age, the most common injection-site reactions observed in clinical studies with AFLURIA were pain, redness, and swelling. The most common systemic adverse events were headache, myalgia, malaise, and fever.

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies with AFLURIA were tenderness and pain. The most common systemic adverse reactions observed were headache, malaise, and muscle aches.

In adults 65 years of age and older, the most common injection-site adverse reactions observed in clinical studies with AFLURIA were tenderness and pain.

Vaccination with AFLURIA may not protect all individuals.

Please see the adjacent Brief Summary of the Prescribing Information.



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AFLURIA® (Influenza Virus Vaccine)

BRIEF SUMMARY (For full Prescribing Information, see Package Insert)

INDICATIONS AND USAGE

AFLURIA is an inactivated influenza virus vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. AFLURIA is approved for use in persons 5 years of age and older.

DOSE AND ADMINISTRATION

For intramuscular (IM) injection only (0.5 mL).

Dose and Schedule

Children

Children 5 years through 8 years of age not previously vaccinated with an influenza vaccine, or vaccinated for the first time last season with only one dose: Administer two 0.5 mL doses, one on Day 1 and another approximately 4 weeks later. Children 5 years through 8 years of age given two doses last season, or at least one dose two or more years ago: Administer a single 0.5 mL dose.

Children 9 years of age and older: Administer a single 0.5 mL dose.

Adults

Administer a single 0.5 mL dose.

Administration

The preferred site for intramuscular injection is the deltoid muscle of the upper arm.

CONTRAINDICATIONS

AFLURIA is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis), to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine (see *Description [11]*).

WARNINGS AND PRECAUTIONS

Fever and Febrile Seizures

Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with postmarketing reports of increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years; these increased rates were confirmed by postmarketing studies. Febrile events were also observed in children 5 to less than 9 years of age.

Guillain-Barré Syndrome (GBS)

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

Preventing and Managing Allergic Reactions

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

Altered Immunocompetence

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

Limitations of Vaccine Effectiveness

Vaccination with AFLURIA may not protect all individuals.

ADVERSE REACTIONS

In children 5 through 17 years of age, the most common injection-site reactions observed in clinical studies with AFLURIA were pain ($\geq 60\%$), redness ($\geq 20\%$) and swelling ($\geq 10\%$). The most common systemic adverse events were headache, myalgia ($\geq 20\%$), malaise and fever ($\geq 10\%$).

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies with AFLURIA were tenderness ($\geq 60\%$) and pain ($\geq 40\%$). The most common systemic adverse events observed were headache, malaise, and muscle aches ($\geq 20\%$).

In adults 65 years of age and older, the most common injection-site adverse reactions observed in clinical studies with AFLURIA were tenderness ($\geq 30\%$) and pain ($\geq 10\%$).

Clinical Trials Experience

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

Children

In clinical studies, AFLURIA has been administered to, and safety information collected for, 3,009 children ages 6 months to less than 18 years. Clinical safety data for AFLURIA in children is presented from three clinical studies (Studies 1, 2, and 3). Data from a comparator-controlled trial (Study 1) are presented, followed by pooled data from two open label studies (Studies 2 and 3). Subjects 6 months through 8 years of age received one or two vaccinations as determined by previous vaccination history (for further details on clinical study design, dosing and demographics see *Clinical Studies [14]*). Study 1 included 1,468 subjects for safety analysis, ages 6 months to less than 18 years, randomized to receive AFLURIA (735 subjects) or another U.S.-licensed trivalent inactivated influenza vaccine (manufactured by Sanofi Pasteur, Inc.) (733 subjects).

Study 2 included 1,976 subjects for safety analysis, ages 6 months to less than 18 years. All subjects received AFLURIA. Study 3 included 298 subjects for safety analysis, ages 6 months to less than 9 years. All subjects received AFLURIA.

The safety assessment was similar for the three pediatric studies. Local (injection site) and systemic adverse events were solicited for 7 days post-vaccination (Tables 1 and 2 in the Prescribing Information). Unsolicited adverse events were collected for 30 days post-vaccination. All adverse events are presented regardless of any treatment causality assigned by study investigators.

Among the pediatric studies, there were no vaccine-related deaths or vaccine-related serious adverse events reported in children 5 years of age and older.

In the comparator-controlled trial (Study 1), the rate of fever after the first dose of AFLURIA in subjects aged 5 to less than 9 years was 16% as compared to 8% in subjects who received the comparator. The rate of fever in subjects aged 9 to less than 18 years following a single dose of AFLURIA was 6% as compared to 4% in subjects who received the comparator. In all three pediatric studies, the rates of fever in subjects aged 5 to less than 9 years who received AFLURIA were lower after dose 2 than dose 1.

The data below are presented for children 5 years and older.

Proportion of Subjects 5 Through 17 Years of Age With Solicited Local or Systemic Adverse Events Within 7 Days After First or Second Dose of AFLURIA, Irrespective of Causality (Study 1)

The most common solicited adverse reactions ($>20\%$) in Study 1 were pain, redness, myalgia, malaise, and headache (subjects aged 5 years to less than 9 years of age) and pain, myalgia, malaise, and headache (subjects aged 9 years to less than 18 years).

Proportion of Subjects 5 Through 17 Years of Age With Unsolicited Adverse Events (Study 1)

In Study 1, unsolicited adverse events that occurred in $\geq 5\%$ of subjects who received AFLURIA in ages 5 years to less than 9 years following the first or second dose included cough (15%) and pyrexia (9%). Unsolicited adverse events that occurred in $\geq 5\%$ of subjects who received AFLURIA in ages 9 years to less than 18 years following the first dose included cough (7%), oropharyngeal pain (7%), headache (7%), and nasal congestion (6%).

Proportion of Subjects 5 Through 17 Years of Age With Solicited Local or Systemic Adverse Events Within 7 Days After Administration of AFLURIA, Irrespective of Causality (Studies 2 and 3)

The most common solicited adverse reactions ($>20\%$) in Studies 2 and 3 were pain and erythema (subjects aged 5 years to less than 9 years of age) and pain, headache, and general muscle ache (subjects aged 9 years to less than 18 years).

Proportion of Subjects 5 Through 17 Years of Age With Unsolicited Adverse Events (Studies 2 and 3)

In Studies 2 and 3, unsolicited adverse events that occurred in $\geq 5\%$ of subjects ages 5 years to less than 9 years after the first or second dose included the following: upper respiratory tract infection (13%), cough (10%), rhinorrhea (7%), headache (5%), nasopharyngitis (5%) and pyrexia (5%). Unsolicited adverse events that occurred in $\geq 5\%$ of subjects who received AFLURIA in ages 9 years to less than 18 years following the first dose included upper respiratory tract infection (9%) and headache (8%).

Adults

In clinical studies, a single dose of AFLURIA was administered to, and safety information collected for, 11,104 subjects ages 18 to less than 65 years and 836 subjects ages 65 years and older. Clinical safety data for AFLURIA in adults are presented from three clinical studies (Studies 4 through 6). In all adult studies, there were no vaccine-related deaths or vaccine-related serious adverse events reported.

Study 4 included 1,357 subjects for safety analysis, ages 18 to less than 65 years, randomized to receive AFLURIA (1,089 subjects) or placebo (268 subjects) (see *Clinical Studies [14]*).

Study 5 included 15,020 subjects for safety analysis, ages 18 to less than 65 years, randomized to receive AFLURIA (10,015 subjects) or placebo (5,005 subjects) (see *Clinical Studies [14]*).

Study 6 included 1,266 subjects for safety analysis, ages 65 years and older, randomized to receive AFLURIA (630 subjects) or another U.S.-licensed trivalent inactivated influenza vaccine (manufactured by Sanofi Pasteur SA) as an active control (636 subjects) (see *Clinical Studies [14]*).

The safety assessment was identical for the three adult studies. Local (injection-site) and systemic adverse events were solicited for 5 days post-vaccination (Table 3). Unsolicited adverse events were collected for 21 days post-vaccination. All adverse events are presented regardless of any treatment causality assigned by study investigators.

Proportion of Subjects 18 Years of Age and Older With Solicited Local or Systemic Adverse Events Within 5 Days After Administration of AFLURIA or Placebo, Irrespective of Causality (Studies 4, 5, and 6)

In Studies 4, 5, and 6, the solicited local or systemic adverse events that occurred in $\geq 20\%$ of subjects who received AFLURIA (regardless of causality) were as follows:

Study 4: tenderness (pain on touching), pain without touching, headache, malaise.

Study 5: tenderness (pain on touching), pain without touching, headache, malaise, muscle aches.

Study 6: tenderness (pain on touching).

Proportion of Adult Subjects With Unsolicited Adverse Events (Studies 4, 5, and 6)

In Study 4, headache was the only unsolicited adverse event that occurred in $\geq 5\%$ of subjects who received AFLURIA or placebo (8% versus 6%, respectively).

In Study 5, headache was the only unsolicited adverse event that occurred in $\geq 5\%$ of subjects who received AFLURIA or placebo (12% versus 11%, respectively).

In Study 6, unsolicited adverse events that occurred in $\geq 5\%$ of subjects who received AFLURIA included headache (8%), nasal congestion (7%), cough (5%), rhinorrhea (5%), and pharyngolaryngeal pain (5%).

Postmarketing Experience

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

Blood and lymphatic system disorders

Transient thrombocytopenia

Immune system disorders

Allergic reactions including anaphylactic shock and serum sickness

Nervous system disorders

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

Vascular disorders

Vasculitis with transient renal involvement

Skin and subcutaneous tissue disorders

Pruritus, urticaria, and rash

Adverse Reactions Associated With Influenza Vaccination

Anaphylaxis has been reported after administration of AFLURIA. Egg protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, asthma, and systemic anaphylaxis (see *Contraindications [4]*).

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

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

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

DRUG INTERACTIONS

Concurrent Use With Other Vaccines

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

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

Concurrent Use With Immunosuppressive Therapies

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B: A reproductive and developmental toxicity study has been performed in female rats at a dose approximately 265 times the human dose (on a mg/kg basis) and revealed no evidence of impaired female fertility or harm to the fetus due to AFLURIA. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, AFLURIA should be given to a pregnant woman only if clearly needed.

In the reproductive and developmental toxicity study, the effect of AFLURIA on embryo-fetal and pre-weaning development was evaluated in pregnant rats. Animals were administered AFLURIA by intramuscular injection twice prior to gestation, once during the period of organogenesis (gestation day 6), and once later in pregnancy (gestation day 20), 0.5 mL/rat/occasion (approximately a 265-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

Nursing Mothers

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

Pediatric Use

AFLURIA is not approved for use in children less than 5 years of age. In a clinical study in which children received AFLURIA or a US-licensed comparator vaccine (Study 1, see *Clinical Trials Experience, [6.1]*), the incidence of fever in children 6 months to less than 3 years of age following the first and second doses of AFLURIA were 37% and 15%, respectively, as compared to 14% following each dose in the comparator group. Among children 3 years to less than 5 years of age, the incidence of fever following the first and second doses of AFLURIA were 32% and 14%, respectively, as compared to 11% and 16% in the comparator. In an open-label study (Study 2), fever, irritability, loss of appetite, and vomiting/diarrhea occurred more frequently in children 6 months to less than 3 years of age as compared to older children. Across three pediatric studies of AFLURIA (Studies 1, 2, and 3), 1.2% of eligible children (n=1,764) were discontinued from the second vaccination because of severe fever ($\geq 104^\circ\text{F}$) within 48 hours of the first vaccination. Across the three pediatric studies, two children, a 7-month old and a 3-year old, experienced vaccine-related febrile seizures (rate of 0.07% across studies), one of which was serious.

Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with increased rates of fever and febrile seizures, predominantly in children below the age of 5 years as compared to previous years, in postmarketing reports confirmed by postmarketing studies (see *Warnings and Precautions [5.1]*).

Geriatric Use

In clinical studies, AFLURIA has been administered to, and safety information collected for, 836 subjects ages 65 years and older (see *Clinical Trials Experience [6.1]*). After administration of AFLURIA, hemagglutinating-inhibiting antibody responses in persons 65 years of age and older were lower as compared to younger adult subjects (see *Clinical Studies [14]*).

HOW SUPPLIED/STORAGE AND HANDLING

Presentation:	Carton NDC Number	Components
Pre-Filled Syringe	33332-012-01	Ten 0.5 mL single-dose syringes without needles [NDC 33332-012-02]
Multi-Dose Vial	33332-112-10	One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-112-11]

Store refrigerated at 2–8°C (36–46°F). Do not freeze. Discard if product has been frozen. Protect from light. Do not use AFLURIA beyond the expiration date printed on the label. Once the stopper of the multi-dose vial has been pierced, the vial must be discarded within 28 days.

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

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



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which was published in the March 2005 issue of the *American Journal of Therapeutics*, there is no evidence that acetaminophen at therapeutic doses aggravates liver disease. Instead, studies have shown that patients with liver disease are able to metabolize acetaminophen appropriately.¹²

MYTH: There are no effective medical treatments for HCV.

FACT: There are effective treatments for both acute and chronic HCV. Patients with acute HCV have an excellent chance of responding to six months of standard therapy with interferon (IFN). And, while IFN should result in spontaneous resolution, there is not a definitive time for when therapy should be started. However, waiting two to four months after the onset of illness is common.

Treatment for chronic HCV has evolved over the years. Initially, studies used IFN monotherapy. Today, treatment is a combination therapy consisting of Ribavirin and IFN or IFN to which polyethylene glycol (PEG) molecules have been added (PEG-IFN). A third feature of combination therapy that is emerging is protease inhibitors. The first protease inhibitor indicated for use in HCV infection, boceprevir (Victrelis), was approved by the U.S. Food and Drug

Administration in May 2011.

There are two goals of chronic HCV treatment. The first is to achieve sustained eradication of HCV, which is defined as the persistent absence of HCV RNA in serum for six months or more after antiviral treatment. The second is to prevent progression to cirrhosis, hepatocellular carcinoma (HCC) and decompensated liver disease requiring liver transplantation.

Patients with HCV-related decompensated cirrhosis should be referred for consideration of liver transplantation.¹³

For physicians, knowing the genotype of HCV can be helpful in making a therapeutic recommendation. Individuals with HCV genotypes 2 and 3 are almost three times more likely than individuals with genotype 1 to respond to IFN monotherapy and combination therapy.¹⁴ Unfortunately, viral superinfections are common causes of treatment resistance.¹⁰

MYTH: Everyone with chronic HCV should be treated for the disease.

FACT: Not every person with chronic HCV will benefit from treatment, and antiviral therapy should be determined on a case-by-case basis. Those most widely recommended for treatment are patients with elevated serum ALT levels who are

older than 18, have positive HCV antibody and serum HCV RNA test results, have compensated liver disease, have acceptable hematologic and biochemical indices (hemoglobin at least 13 g/dL for men and 12 g/dL for women; neutrophil count greater than 1,500/mm³ and serum creatinine less than 1.5 mg/dL), a willingness to be treated and to adhere to treatment requirements, and no contraindications for treatment. A further criterion is liver biopsy findings consistent with a diagnosis of HCV; however, a pretreatment liver biopsy is not mandatory.¹³

There are effective treatments for both acute and chronic HCV.

Individuals not suitable for combination therapy are those who cannot tolerate side effects or who have contraindications to IFN or Ribavirin therapy. For instance, individuals who have low values of red and white blood cells and platelets may not be able to tolerate IFN therapy safely. In addition, IFN therapy may affect the brain, so it is not given to individuals who have a seizure disorder that cannot be controlled with anti-epileptic therapy, and it is thought unwise to use IFN therapy in individuals who have some immune disorders, particularly those with autoimmune diseases, for fear of it causing a flare-up of the disease. Because of Ribavirin's side effects, it should never be given to individuals who would become rapidly unwell with a sudden fall in hemoglobin, such as those who have poor oxygen supply to their heart or brain from hardening of arteries. Ribavirin also should not be given to individuals with renal failure. And, because Ribavirin is damaging to the unborn child (teratogenic), neither a male nor female may impregnate or conceive during treatment and for six months after stopping treatment.¹⁵

MYTH: Most people can't be treated for HCV because they can't tolerate the side effects.

FACT: Some patients can't tolerate HCV therapy for a variety of reasons, including side effects, but these people are the exception rather than the rule. However, the inability to tolerate side effects can be a cause of failure to complete therapy. Fortunately, there have been dramatic improvements in the way that side effects are managed.

Many of the side effects of therapy superimpose upon the pre-existing fatigue, depression, nausea and myalgias (muscle aches) that already plague the HCV patient. The most serious side effects are changes in the hematologic system. Other side

effects include depression, anxiety, insomnia, headaches, muscle aches and skin rashes. Depression and anxiety often become the most troublesome problems for patients, particularly in those with pre-existing problems. For all of these side effects, there are other medications available to counteract them.¹⁶

Dispelling the Myths Now

The medical profession has had little more than a quarter of a century to understand HCV, but diagnosis and treatment have come a long way. Unfortunately, for patients and others, many myths about the disease exist that lead to fear and make living with HCV even more difficult. Fortunately, HCV is not a death sentence for most. Only 10 percent to 25 percent of people chronically infected with HCV will experience serious liver disease progression that may result in death. The remaining 75 percent to 90 percent will live long and productive lives⁸ — as long as the facts about HCV are understood. ❖

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

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INTRODUCING

Kedrion Biopharma

KEEP LIFE FLOWING

Kedrion Biopharma is a biopharmaceutical company with 40 years of dedication to human plasma-based therapies within:

- Critical Care
- Hematology
- Immunology
- Transfusion Medicine
- Women's Health

KEDRION
B I O P H A R M A

A Vision for Global Leadership

“Our corporate culture is built upon promoting the social value of plasma processing for the treatment of chronic disease, and ultimately improving the quality of people’s lives.”

— Paolo Marcucci, President and CEO, Kedrion

BY TRUDIE MITSCHANG

AS A LEADING global biopharmaceutical company specializing in the development, production and distribution of plasma-derived products, Kedrion is a name that is well-respected throughout Europe and beyond. Headquartered in Italy, Kedrion has an established presence in Europe, Mexico and the United States, with a workforce boasting more than 1,400 employees. The company’s core offerings include immune globulins (standard and hyperimmune), coagulation factors (factor VIII, factor IX), coagulation inhibitor (antithrombin III) and albumin — all of which are distributed in 60 countries around the world.

At the helm of this rapidly expanding organization is President and CEO Paolo Marcucci. Marcucci has held key positions within Kedrion for the past decade, including serving as CEO of Kedrion Biopharma, a subsidiary of Kedrion Group operating in the U.S. market. A visionary leader, Marcucci’s focus has been on defining the best practices that will support Kedrion’s expansion in global markets, and the consolidation of the company’s presence within North America. “Our goal is to continually strengthen our worldwide role as a strategic partner of the

national health systems, especially for countries that would like to become more cost effective, and to make products available to meet the needs of countries belonging to emerging markets,” Marcucci says. “Our corporate culture is built upon promoting the social value of plasma processing for the treatment of chronic diseases, and ultimately improving the quality of people’s lives.”

Promoting Supply Chain Safety

Kedrion has developed a plasma processing model that is both efficient and diversified; the company currently owns nine fully operational collection centers in the U.S., three in Germany (Bavaria) and another three in Hungary. Marcucci notes that Kedrion’s state-of-the-art production facilities are certified according to Good Manufacturing Practices and are based on U.S. Food and Drug Administration (FDA) requirements. “At Kedrion, we put safety and quality as the starting points of everything we do,” Marcucci says. “Our highly detailed internal processes guarantee the quality, effectiveness and purity of our products from start to finish.”



In an effort to maximize safety for the patients on the receiving end of its plasma products, Kedrion utilizes a detailed checklist dubbed the Kedrion Quality Program (KQP). The eight-step safety protocol ensures the ongoing monitoring of every phase of the manufacturing process, including in-depth testing of each plasma donation, inventory hold and look-back procedures, and validated viral removal and inactivation steps. In addition, Kedrion’s plants are regularly inspected by regional health authorities to check and certify that they comply with industry regulations and standards.

Pursuing Innovation and Social Responsibility

Long recognized for its leadership in the area of innovation, Kedrion was honored in recent years when its production plant in Sant’Antimo was

toured by Luigi Nicolais, Italy's Minister of Reform and Innovation in the Public Administration. During the visit, Marcucci met with Nicolais to outline the company's growth strategy, particularly Kedrion's ongoing efforts to improve its manufacturing process and the organization's investments in infrastructure and staff at the manufacturing site, currently recognized as a national center of excellence. "For those who work in a field where industry meets science, the presence of Hon. Nicolais, one of the most respected Italian researchers in the world, was extremely rewarding," Marcucci notes.

A commitment to social responsibility is one of Kedrion's core values, and under Marcucci's leadership, the company has implemented an organizational structure that includes an ethical committee, an ethical officer and code of conduct safeguards to ensure its values are practiced throughout the organization.

An active supporter of patients and patient advocacy organizations, Kedrion recently donated more than one million units of coagulation factor to the Save One Life organization, which used the medicines to treat patients in Pakistan. In late 2012, Kedrion also helped fund the creation of the first Jeffrey Modell Paediatric Immunology Centre in Italy. In addition to its three-year funding commitment, Kedrion will support the project through research and product development. "With the birth of Italy's first JMF Paediatric Immunology Centre, Kedrion shows its commitment and support to young patients suffering from immune deficiencies and our dedication to scientific research and education in this field," Marcucci explains. "We believe in investing in people, innovation and research to support the medical and scientific communities and patient organizations, with the ultimate goal of making plasma products more widely available."



Promise in the Pipeline

As he looks to the future, Marcucci is excited about Kedrion's support of a number of orphan drug research and development projects in partnership with several public and private sector organizations. The plasma proteins being researched include plasminogen for the treatment of ligneous conjunctivitis, factor II for the treatment of prothrombin deficiencies, factor V for the treatment of factor V deficiencies (parahaemophilia), and factor H for the treatment of hemolytic uremic syndrome (HUS) and type II membranoproliferative glomerulonephritis.

"It is rewarding to know that our daily efforts have a positive effect on the quality of life for individuals living with life-altering disease," Marcucci says. "Our investment in research and development supports our belief in what we refer to as the 'Universal Declaration of Human Rights,' which is the right of every human being to live in the best possible conditions. By collecting, converting and making usable the vital energy generated and carried through blood, we can support this fundamental right." ❖

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

XLA: A Patient's Perspective

The Johnsons look like a picture-perfect family, but behind the smiles, this family faces the daily challenges, heartbreak and loss that come with a diagnosis of primary immunodeficiency.

BY TRUDIE MITSCHANG

LIKE ANY YOUNG couple, college sweethearts Jessica and Bart Johnson dreamed of starting a family. More than a decade later, Christmas card photos show a picture-perfect clan: Emma, 11, Andy, 9, Matthew, 5, and Gavin, 3. But the smiling faces don't tell the whole story; missing from the photo is their third child, Ethan, who passed away in 2006 from complications caused by X-linked agammaglobulinemia (XLA), a rare primary immunodeficiency.

The Johnsons' first son, Andy, was frequently sick with colds and sinus infections. Although Jessica suspected something was wrong, she assumed an immune system problem would have been diagnosed during newborn screenings. But when Ethan was born two years later and displayed the same symptoms, she grew concerned. Ethan was 8 months old when he and Andy contracted septic adenovirus infections and were sent to the University of Minnesota Hospital, where they were diagnosed with pneumonia and an uncommon but serious blood disorder called hemophagocytic lymphohistiocytosis. By the time doctors identified XLA as the underlying cause, Ethan tragically succumbed to his infections. Thankfully, physicians were able to save Andy.

Understanding and Treating XLA

XLA was one of the first immunodeficiency diseases ever identified. First described in 1952 by Dr. Ogden Bruton, XLA is sometimes called Bruton's



Jessica and Bart Johnson have four children, three of whom have X-linked agammaglobulinemia. Their fifth child succumbed to the disease when he was an infant.

agammaglobulinemia or congenital agammaglobulinemia. XLA is rare; it is estimated that only one in 200,000 babies will be diagnosed. Jessica and Bart were told it occurred in one out of every four births when the mother is a carrier, so after two of their boys were born with XLA, it seemed the odds were in their favor. As the couple soon learned, that was not to be. "We had two more boys after Ethan passed away, and both of them have XLA," says Jessica. "We ended up with four out of five; our oldest child, Emma, is healthy."

Managing Treatment

XLA is an inherited immunodeficiency disease in which patients lack the ability to produce antibodies; however, patients can be given some of the antibodies that they are lacking in the form of immune globulin (IG) administered intravenously (IVIG) or subcutaneously (SCIG). Jessica

administers SCIG to her boys at home, a method she finds fits best with her busy family. "We do infusions every Friday," she explains. "When Andy was first diagnosed, he had a Hickman catheter, and he got IVIG once a month with a nurse. Once the catheter was removed, I started doing SCIG infusions myself — each time I had a new baby with XLA, I just added them to the lineup."

Accepting a New Normal

Raising four children is a daunting undertaking, even under the best of circumstances. When three of those kids live with a chronic illness, the task can feel overwhelming. Jessica and Bart say surviving the loss of a child has helped them put everyday concerns into perspective. "The little things that used to send me through the roof with worry are no longer that big of a concern," says Jessica, who adds that other than the infusions, their lives are fairly normal. "Every day I wake Andy up first, because he has to do a half-hour treatment with his Vest Airway Clearance System. His pneumonia was so bad when he was little that it permanently damaged some of his lung tissue. Then I get Emma and Andy off to the bus stop and spend the rest of the day running after Matthew and Gavin. After school, we're doing sports, piano lessons, homework and supper, not necessarily in that order!" ♦

TRUDIE MITSCHANG is a staff writer for BioSupply Trends Quarterly.

XLA: A Physician's Perspective

Prior to penicillin, life expectancy was limited for patients with X-linked agammaglobulinemia. Thanks to the advent of intravenous immune globulin, the prognosis today is much more promising.



Hans D. Ochs, MD, is professor of pediatrics at the University of Washington School of Medicine in Seattle, Wash.

HANS D. OCHS, MD, is a respected researcher whose emphasis has been on the molecular basis of primary immune deficiency diseases (PIDDs) with special interest in the genes linked to Wiskott-Aldrich syndrome, hyper-IgM syndromes, IPEX syndrome, autosomal recessive hyper-IgE syndrome and X-linked agammaglobulinemia (XLA).

Dr. Ochs started the Immunodeficiency Clinic in 1985 at Seattle Children's Hospital, providing evaluation and care for both pediatric and adult patients with immunodeficiency disorders. He is principal investigator for the U.S. Immune Deficiency Network (USIDnet) and co-founder and member of the summer school faculty devoted to PIDDs. He also is principal editor for the medical

textbook *Primary Immunodeficiency Diseases: A Molecular and Genetic Approach* and co-editor of *Immunological Disorders in Infants and Children*.

BSTQ: What is XLA?

Dr. Ochs: XLA, which is also referred to as Bruton's agammaglobulinemia or congenital agammaglobulinemia, was the first immunodeficiency disease ever identified. "X-linked" means that the gene that causes this agammaglobulinemia is located on the X chromosome and therefore primarily affects males, since it is unlikely that females will have two altered copies of the gene.

BSTQ: What are the effects of the disease?

Dr. Ochs: The disease causes the patient to be unable to produce antibodies that make up gammaglobulins in the plasma portion of blood. In XLA, there is a failure of pre-B lymphocytes to mature into B lymphocytes (mature B lymphocytes produce antibodies). Since a patient with XLA produces no antibodies, they are unable to fight off bacterial infections and some viral infections.

BSTQ: What causes XLA?

Dr. Ochs: XLA is caused by inheriting a faulty gene located on the X chromosome. Humans normally have 46 total chromosomes, or 23 pairs in each cell of their body. The 23rd pair determines gender; females have two X chromosomes, and males have one X and one Y chromosome. When females have a disease-causing gene on one of their X chromosomes but do not exhibit any symptoms of the disease, they are referred to as carriers. Males, on the

other hand, have only one X chromosome. So if their X chromosome carries a disease-causing gene, then they will exhibit symptoms of the disease. Carrier females have a 50/50 chance with each pregnancy to pass the X chromosome with the faulty gene to a child. If a daughter receives the gene, she will be a healthy carrier like the mother. However, if a son receives the gene, he will have XLA.

BSTQ: Can parents be tested for XLA?

Dr. Ochs: Women can undergo molecular genetic testing of the BTK gene, in addition to prenatal diagnosis (amniocentesis or chorionic villus sampling) for pregnancies when the mother is a known carrier.

BSTQ: How is XLA diagnosed?

Dr. Ochs: Diagnosis is usually made based on a complete medical history and physical examination of the child. In addition, multiple blood tests may be ordered to help confirm the diagnosis.

BSTQ: What's the long-term outlook for a child with XLA?

Dr. Ochs: Without antibody replacement, these children could die at an early age from severe infections. Children who develop chronic lung disease with bronchiectasis (widening and scarring of the airways) may have a shortened life span in some cases. The good news is, thanks to the availability of immune globulin infusions, children diagnosed and treated early can definitely lead normal, active lives. ❖

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

The Plasma Industry: Investing Today to Ensure IgG and Albumin Supply for Tomorrow

BY KEITH BERMAN, MPH, MBA

BEHIND ALL THE vials of immune globulin (IG) waiting on the pharmacy shelf are two important behind-the-scenes activities that make it possible: long-term manufacturer commitments to invest in new production capacity, and the willingness of many thousands of new donors to contribute very large quantities of blood plasma, the sole raw material from which this product is purified.

Consider an adult patient about to receive a 30-gram dose of intravenous immune globulin (IVIG) given as IgG replacement therapy. About 3.5 to 4 grams of IgG can be purified from each liter of plasma. Thus, around 10 plasma donations, each averaging about 750 milliliters, go into producing that single dose. Another common dose used for treatment of certain autoimmune disorders — one gram per kilogram body weight — requires collection of roughly 18 to 20 liters from at least 25 “source” plasma donations obtained by carefully supervised plasmapheresis at a licensed plasma collection center.*

Global Demand Grows, Industry Responds

Now consider what those plasma requirements mean in the context of more than two decades of steady, uninterrupted growth in IG demand. From worldwide IVIG product sales of about

16 million grams in 1990, expanding numbers of clinical indications and increasing physician awareness drove sales to about 47 million grams by 2000. And, global demand continued to climb, doubling to 95 million grams by 2010 (see Figure 1). Just over the five-year period from 2006 through 2011, global

als, increase scheduled production runs or build more manufacturing capacity, and add filling lines and perhaps some warehouse capacity for storage of finished goods. But for manufacturers of human plasma-based therapeutics, that unique raw material creates dynamics that are anything but typical.

Securing additional IgG-rich plasma requires expanding the existing network of plasma collection centers.

sales of IVIG and subcutaneous IG (SCIG) products have jumped from 69 million grams to just over 107 million grams — an average of nearly 10 percent annually, according to Patrick Robert of The Marketing Research Bureau (MRB), a Connecticut-based firm that tracks and reports market data for all therapeutic plasma products. Global demand for human albumin solutions used in surgeries, shock and a variety of other settings has increased more than 50 percent over the last decade.

For most sectors of the drug industry, supply readiness to meet this rate of demand growth is straightforward: Contract to purchase more raw materi-

Securing additional IgG-rich plasma requires expanding the existing network of plasma collection centers. To keep up with 10 percent annual growth in demand translates into recruiting tens of thousands of new donors and performing upwards of three million additional plasma donation procedures each year. As the siting, construction, staffing and securing of regulatory approvals to operate a single new collection center can require up to two years, demand growth must be forecasted and investments made well in advance to assure that extra plasma is collected and ready for manufacturing when it's needed.

* Alternatively, those 30 grams can be purified from “recovered plasma” collected from around 25 screened and tested whole blood donations; each average half-liter unit of blood yields about 250-300 milliliters of plasma.

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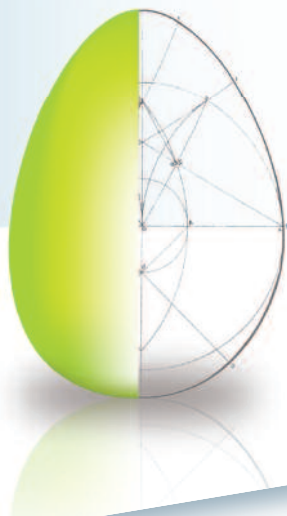
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Important Safety Information

Privigen is indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

WARNING: Use of Immune Globulin Intravenous (IVIg) products, particularly those containing sucrose, have been associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Privigen does not contain sucrose. Administer Privigen at minimum rate practicable in patients at risk of renal dysfunction or acute renal failure. At-risk patients include those with preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; over 65 years of age; or receiving known nephrotoxic drugs. See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperproteinemia, and in IgA-deficient patients with antibodies to IgA and history of hypersensitivity.

Monitor patient vital signs throughout infusion of Privigen. In cases of severe hypersensitivity or anaphylactic reactions, discontinue administration and institute appropriate medical treatment. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have occurred in patients with risk factors; consider baseline assessment of blood viscosity for those at risk of hyperviscosity. Patients could experience increased serum viscosity,

hyperproteinemia or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur (most often with high doses and/or rapid IVIg infusion).

Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to treatment with Privigen. Closely monitor patients for hemolysis and hemolytic anemia. Risk factors for hemolysis include non-O blood group, underlying inflammation, and high doses. Carefully consider relative risks and benefits before prescribing high-dose regimen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload.

Monitor patients for pulmonary adverse reactions and signs of transfusion-related acute lung injury (TRALI).

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

In clinical studies of patients being treated with Privigen for PI, the most serious adverse reaction was hypersensitivity (one subject). Adverse reactions observed in >5% of subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

In clinical studies of patients being treated with Privigen for chronic ITP, the most serious adverse reactions were AMS (one subject) and hemolysis (eight subjects). Adverse reactions seen in >5% of subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, increases in conjugated and unconjugated bilirubin, hyperbilirubinemia, and increased blood lactate dehydrogenase.

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing.

Please see brief summary of full prescribing information on following pages.

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

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

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

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

4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have a history of anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Privigen is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (see *Description* [11]).
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (see *Warnings and Precautions* [5.1]).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

Privigen contains trace amounts of IgA (≤ 25 mcg/mL) (see *Description* [11]). Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Privigen. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity.

5.2 Renal Dysfunction/Failure

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

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.¹ If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Privigen at the minimum rate of infusion practicable (see *Boxed Warning, Dosage and Administration* [2.3]).

5.3 Thrombotic Events

Thrombotic events may occur following treatment with IGIV products, including Privigen.²⁻⁴

Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/ suspected hyperviscosity.

Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable (see *Dosage and Administration* [2.3]).

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.⁵

5.5 Aseptic Meningitis Syndrome (AMS)

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

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct

a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

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

5.6 Hemolysis

Privigen may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs' test) result and hemolysis.⁷⁻⁹ Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.¹⁰ Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of Privigen.

The following can be associated with risk of hemolysis: high doses (eg, ≥ 2 g/kg), whether given either as a single administration or divided over several days; non-O blood group; and underlying inflammatory state.^{11,12} Hemolysis has been reported following administration of IGIV for indications including ITP AND PI.

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

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen.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. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) antibodies in both the product and the patient's serum.

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

5.8 Volume Overload

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

5.9 Transmissible Infectious Agents

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

Report any infection thought to be possibly transmitted by Privigen to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.10 Interference with Laboratory Tests

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

6 ADVERSE REACTIONS

The most serious adverse reactions observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >5% of clinical study subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data. The most common adverse reactions observed in >5% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, hyperthermia, bilirubin conjugated increased, bilirubin unconjugated increased, hyperbilirubinemia, and blood lactate dehydrogenase increased.

6.1 Clinical Trials Experience

Because different 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.

Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study (pivotal study), 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen every 3 or 4 weeks for up to 12 months (see *Clinical Studies* [14.1]). All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 34 (42.5%) were female.

The safety analysis included all 80 subjects, 16 (20%) on the 3-week schedule and 64 (80%) on the 4-week schedule. The median dose of Privigen administered was 428.3 mg/kg (3-week schedule) or 440.6 mg/kg (4-week schedule) and ranged from 200 to 888 mg/kg. A total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule.

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during an infusion or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2: PI Pivotal Study – Adverse Events Occurring in >5% of Subjects During a Privilgen Infusion or Within 72 Hours After the End of an Infusion, Irrespective of Causality

Adverse Event (Excluding Infections)	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Event [n=1038]
Headache	35 (43.8)	82 (0.079)
Pain	20 (25.0)	44 (0.042)
Fatigue	13 (16.3)	27 (0.026)
Nausea	10 (12.5)	19 (0.018)
Chills	9 (11.3)	15 (0.014)
Vomiting	7 (8.8)	13 (0.013)
Pyrexia	6 (7.5)	10 (0.010)
Cough	5 (6.3)	5 (0.005)
Diarrhea	5 (6.3)	5 (0.005)
Stomach discomfort	5 (6.3)	5 (0.005)

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be at least possibly related to the infusion of Privilgen (including 5 serious, severe AEs described below). Of these, 91 were mild, 81 were moderate, 19 were severe, and 1 was of unknown severity.

Table 3: PI Pivotal Study – Adverse Reactions Occurring in >5% of Subjects, Irrespective of Time of Occurrence

Adverse Reaction	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Reaction [n=1038]
Headache	24 (30.0)	62 (0.060)
Pain, all types*	12 (15.0)†	26 (0.025)
Nausea	10 (12.5)	18 (0.017)
Fatigue	9 (11.3)	16 (0.015)
Chills	9 (11.3)	15 (0.014)
Vomiting	6 (7.5)	11 (0.011)

* Includes abdominal pain lower, abdominal tenderness, arthralgia, back pain, chest pain, infusion-site pain, injection-site pain, neck pain, pain, pain in extremity, and pharyngolaryngeal pain.

† Some subjects experienced more than one type of pain.

Sixteen (20%) subjects experienced 41 serious AEs. Five of these AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature, all severe) were related to Privilgen, occurred in one subject, and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privilgen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative DAT at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

An extension of the pivotal study was conducted in 55 adult and pediatric subjects with PI to collect additional efficacy, safety, and tolerability data. This study included 45 subjects from the pivotal study who were receiving Privilgen and 10 new subjects who were receiving another IGIV product prior to enrolling in the extension study. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female.

Subjects were treated with Privilgen at median doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months. Twelve (21.8%) subjects were on a 3-week treatment schedule with the number of infusions per subject ranging from 4 to 38 (median: 8 infusions); 43 (78.2%) subjects were on a 4-week schedule with the number of infusions ranging from 1 to 31 (median: 15 infusions). A total of 771 infusions were administered in this study.

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privilgen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min (see *Dosing and Administration* [2.3]). The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

In this study, the proportion of infusions temporally associated with one or more AEs occurring during a Privilgen infusion or within 72 hours after the end of an infusion was 15%. The total number of temporally associated AEs, *irrespective of causality*, was 206 (a rate of 0.27 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Of the 206 temporally associated AEs reported for the 55 subjects with PI, the investigators judged 125 to be at least possibly related to the infusion of Privilgen. Of these, 76 were mild, 40 were moderate, and 9 were severe.

Eleven (20%) subjects experienced 17 serious AEs, none of which were considered to be related to Privilgen. Three subjects experienced AEs that were considered to be at least possibly related to Privilgen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild urticaria in one subject, resulting in the subject's withdrawal from the study.

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of 20 x 10⁹/L or less received a total of 2 g/kg dose of Privilgen administered as 1 g/kg infusions daily for 2 consecutive days (see *Clinical Studies* [14.2]). Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 6: Chronic ITP Study – Adverse Events Occurring in >5% of Subjects During a Privilgen Infusion or Within 72 hours After the End of a Treatment Cycle, Irrespective of Causality (Two consecutive daily infusions)

Adverse Event	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Event [n=114]
Headache	37 (64.9)	41 (0.360)
Pyrexia/hyperthermia	21 (36.8)	22 (0.193)
Nausea	6 (10.5)	6 (0.053)
Epistaxis	6 (10.5)	6 (0.053)
Vomiting	6 (10.5)	6 (0.053)
Blood unconjugated bilirubin increased	6 (10.5)	6 (0.053)
Blood conjugated bilirubin increased	5 (8.8)	5 (0.044)
Blood total bilirubin increased	4 (7.0)	4 (0.035)
Hematocrit decreased	3 (5.3)	3 (0.026)

Table 7: Chronic ITP Study – Adverse Reactions Occurring in >5% of Subjects, Irrespective of Time of Occurrence

Adverse Reaction	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Reaction [n=114]
Headache	37 (64.9)	52 (0.456)
Pyrexia/hyperthermia	19 (33.3)	21 (0.184)
Positive DAT	6 (10.5)	7 (0.061)
Anemia	6 (10.5)	6 (0.053)
Vomiting	5 (8.8)	6 (0.053)
Nausea	5 (8.8)	7 (0.061)
Bilirubin conjugated, increased	5 (8.8)	5 (0.044)
Bilirubin unconjugated, increased	5 (8.8)	5 (0.044)
Hyperbilirubinemia	3 (5.3)	3 (0.026)
Blood lactate dehydrogenase increased	3 (5.3)	3 (0.026)
Hematocrit decreased	3 (5.3)	3 (0.026)

Of the 149 non-serious AEs related to Privilgen, 103 were mild, 37 were moderate, and 9 were severe.

Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privilgen.

One subject withdrew from the study due to gingival bleeding that was not related to Privilgen. Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privilgen. Two of the eight subjects were clinically anemic but did not require clinical intervention; these cases resolved uneventfully.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privilgen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The following adverse reactions have been identified and reported during the post-approval use of IGIV products.¹²

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

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 Based on May 2012 revision

A still longer lead time is required to assure that there will be manufacturing capacity to purify this new plasma into therapeutic proteins. How long? As an example, Baxter announced last August that it broke ground on a new three million-liter fractionation facility near Atlanta. Construction on this \$1 billion project is expected to be completed by 2017, with commercial production starting in 2018. America will slog through two more congressional election cycles before the first gram of IG or albumin leaves that facility. No other drug or biologic involves new production capacity development lead times like that.

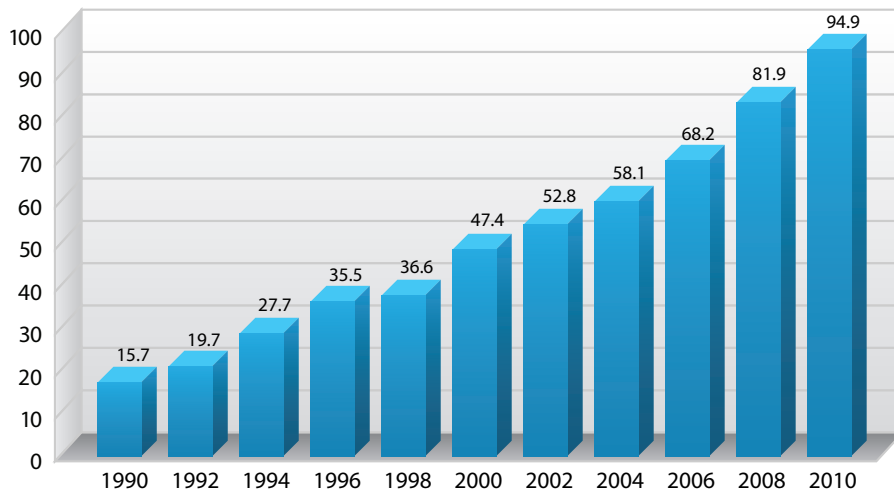
Four companies — Baxter, CSL Behring, Grifols and Octapharma — manufacture and sell more than half of the albumin and nearly two-thirds of the global supply of polyvalent IG products, according to MRB. And as experienced providers know too well, product shortages are both logistically challenging and costly, as prices overall tend to rise. So are these four manufacturers and a handful of other key suppliers keeping pace with fast-growing global demand for these products?

From all indications, the answer is yes. North American source plasma collections, which account for around 60 percent of all plasma fractionated into therapeutics, have more than doubled between 2005 and 2011 (see Figure 2). And the industry has similarly anticipated the need to expand production, adding more than 15 million liters of plasma fractionation capacity over the last decade. Coupled with this, the industry has found ways to significantly improve IgG yield from each liter, further boosting production capacity.

Peering into the Future

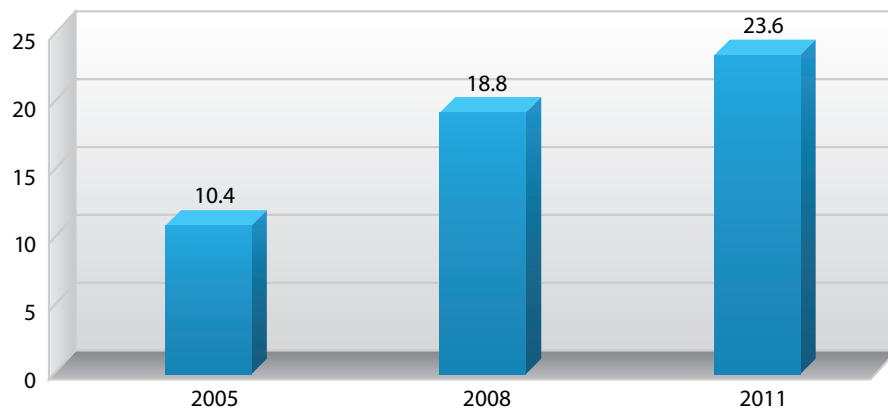
Expanding awareness of the therapeutic benefits of polyvalent IgG and human albumin, together with growing demand in emerging markets such as

Figure 1. Worldwide Intravenous Immunoglobulin (IVIG) Sales from 1990 to 2010 (millions of grams)



Source: The Marketing Research Bureau, Inc.

Figure 2. North American Source Plasma Collections from 1990 to 2010 (millions)



Source: Plasma Protein Therapeutics Association

China and Latin America, will likely extend worldwide demand growth for years to come. In addition, a robust research and development pipeline creates the prospect of important new patient uses. Of particular interest, in light of promising preclinical data and early clinical observations, are trials currently evaluating IVIG and albumin as potential disease-modifying treatments for Alzheimer’s disease and for stroke.

Meanwhile, the plasma industry continues to plan and invest for the

future to assure that immunoglobulin, albumin and other life-critical plasma products are on the shelf when they’re needed. ❖

KEITH BERMAN, MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Since 1989, he has also served as editor of International Blood/Plasma News, a blood products industry newsletter.



Brittney



Joey



Ian



Trevor

Influenza **TAKES** lives...



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Alana



Jessica

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Every year in the United States, 20,000 children are hospitalized and nearly 100 die from influenza and its complications. **Vaccination is safe and effective and is the single best way to protect your patients and their families from influenza.**



Emily

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

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



FAMILIES
FIGHTING FLU, INC.

IVIG as Effective as Plasma Exchange in Treating Guillain Barré Syndrome

In a meta-analysis of seven Cochrane trials to determine the efficacy of intravenous immunoglobulin (IVIG) for treating Guillain Barré syndrome, IVIG was as effective as plasma exchange (PE) in reducing disability scores, with no significant difference in adverse events.

The randomized and quasi-randomized trials with a variable risk of bias compared IVIG with PE in 623 severely affected participants. In five trials with 536 participants for whom the outcome was available, the mean difference (MD) of change in a seven-grade disability scale after four weeks was not significantly different between the two treatments: MD of 0.02 of a grade more improvement in the IVIG than the PE group (95% confidence interval (CI) 0.25 to -0.20). There also were no statistically significant differences in the other measures considered. Three studies including a total of 75 children suggested that IVIG significantly hastens recovery compared with supportive care. In one trial involving 249 participants comparing PE followed by IVIG with PE alone, the mean grade improvement was 0.2 (95% CI -0.14 to 0.54) more in the combined treatment group than in the PE alone group. Another trial with 37 participants comparing immunoabsorption followed by IVIG with immunoabsorption alone did not reveal significant extra benefit from the combined treatment.

Adverse events were not significantly more frequent with either treatment, but IVIG is significantly much more likely to be completed than PE. Small trials in children showed a trend toward more improvement with high-dose compared with low-dose IVIG, and no significant difference when the standard dose was given over two days rather than five days.

Hughes RA, Swan AV, and Van Doorn PA. Intravenous Immunoglobulin for Guillain-Barré Syndrome. Cochrane Database Syst Rev, 2012 Jul 11;7:CD002063.

Study Reveals Clinical Manifestations that Lead to Delayed Diagnosis in CVID Patients

Researchers in a university hospital sought to determine the spectrum of clinical manifestations, immunological characteristics and the time to diagnose patients with common variable immunodeficiency (CVID) disorders. CVIDs represent a heterogeneous disease spectrum that includes recurrent infections and complications such as autoimmunity, inflammatory organ disease and an increased risk of cancer.

A representative cohort study was performed in 61 adult

CVID patients and 18 patients with a partial antibody deficiency (selective antibody deficiency with normal immunoglobulins [SADNI] and IgG subclass deficiency) who met the ESID/PAGID diagnostic criteria for CVIDs, IgG subclass deficiency and SADNI. The researchers found that infections were the main presentation of all antibody-deficient patients, and the number of patients with infections declined during IgG therapy. However, the development of bronchiectasis continued despite IgG therapy, as well as the development of autoinflammatory conditions. Noninfectious disease complications were present in 30 percent of CVID patients at the time of diagnosis, and this increased to 51 percent during follow-up despite IgG therapy. The most common noninfectious disease complications were autoimmunity and lymphoproliferative disease.

The median time to diagnose CVID was 10 years. However, in patients with noninfectious complications, the time to diagnose was considerably longer when compared with the group of patients without complications (17.6 years vs. 10.2 years, $p=0.026$).

Maarschalk-Ellergroek LJ, Hoepelman, AIM, van Montfrans JM, and Ellergroek P. The Spectrum of Disease Manifestations in Patients with Common Variable Immunodeficiency Disorders and Partial Antibody Deficiency in a University Hospital. J Clin Immun, 2012 Oct; 32(5):907-921.

Study Shows New SCIG Drug Safe and Efficacious

Researchers investigated the efficacy, safety and pharmacokinetics and quality of life impact of Evogam, a new chromatographically fractionated 16% subcutaneous immunoglobulin (SCIG). In the Phase III, open-label, multicenter study, 35 primary immunodeficiency patients previously treated with intravenous immunoglobulin received weekly Evogam over 36 weeks. Primary endpoints were rate of serious bacterial infections (SBIs) and steady-state serum immunoglobulin G (IgG) trough concentrations.

No SBIs were reported during the study, and Evogam produced significantly higher mean trough IgG concentrations with a 1:1 dose conversion compared with previous immunoglobulin treatment (8.94 versus 8.27 g/L, $p=0.0063$). The researchers concluded that Evogam is efficacious in the prevention of infections and maintenance of trough levels using a 1:1 dose conversion. It was well-tolerated with no withdrawals due to adverse events, and it was preferred to IVIG by the majority of patients.

Empson MB, Tang MLK, Pearce LKC, Rozen L, Gold MS, et al. Efficacy, Safety and Pharmacokinetics of a Novel Subcutaneous Immunoglobulin, Evogam, in Primary Immunodeficiency. J Clin Immun, 2012 Oct; 32(1):897-906.

BioResources



Recently released resources for the biopharmaceuticals marketplace.



Physician Portal for Genetic Testing Access

Manufacturer: NextGxDx

Healthcare information technology startup NextGxDx has released a free, online platform for physicians through which they can search for genetic tests, compare tests offered by different

labs, order a test and receive results. The platform lists more than 10,000 genetic tests, including those that are approved or cleared by the U.S. Food and Drug Administration, as well as those that are offered through CLIA-certified labs. The goal of the platform is to integrate the rapidly growing world of genetic diagnostics with the day-to-day operations of a clinic, as well as to simplify the workflow and make genetic testing simpler for community doctors to use. Once physicians order tests through the web-based platform, NextGxDx generates a requisition form and processes the order. Then, the order form is sent out of the lab for analysis, and test results are reported back to the physicians through the platform website. The platform is encrypted to protect the privacy of patients, and test results are stored in compliance with HIPAA regulations. Although test results are reported electronically, currently they aren't incorporated into patients' EMRs. There is no cost to physicians for accessing the platform; labs pay a fee to include their test information in the service.

www.nextgxdx.com

role and coverage of the uninsured. It describes Medicaid's appeals system, including the fair hearing process and the appeals process required for Medicaid managed care organizations. As coverage expands under healthcare reform and efforts proceed to integrate services for dual eligibles who are enrolled in both Medicare and Medicaid, protections through the appeals process will be increasingly important.

www.kff.org/medicaid/8287.cfm



ICD-9-CM 2013 Professional Edition for Physicians, Volumes 1 and 2

ICD-9-CM 2013 Professional Edition for Hospitals, Volumes 1, 2 and 3

Author: American Medical Association

These updated 2013 editions deliver important diagnostic coding and reimbursement information.

By integrating the Official Guidelines for Coding and Reporting into the ICD-9-CM code set, these codebooks provide the information physicians and hospitals need to ensure the most accurate billing for their practices. Key features include full-color Frank Netter anatomical plates (that educate users about anatomy), a companion website (which provides the latest updates, an ICD-9-CM to ICD-10-CM crosswalk, and MS-DRG information), coding tips and notes developed by coding experts (which define terms and provide additional coding instruction to aid in understanding difficult terminology, diseases and conditions or coding in a specific category) and the American Hospital Association's Coding Clinic for ICD-9-CM citations (which provides reference information regarding official ICD-9-CM coding advice that will enhance understanding of specific codes). The hospital edition also provides volume 3 procedural codes with professional annotations and highlighted symbols for "unrelated or procedure," "present on admission," "complication and co-morbidity," "major complication and co-morbidity" and "hospital-acquired condition" that may affect DRG assignment and aid in reducing risk of upcoding audits and potential fines.

https://catalog.ama-assn.org/Catalog/product/product_detail.jsp?productId=prod2000011



Kaiser Commission on Medicaid and the Uninsured: A Guide to the Medical Appeals Process

Author: Kaiser Family Foundation's Commission on Medicaid and the Uninsured

This new guide provides a comprehensive look at the appeals process for the Medicaid program, which differs

significantly from those available through the Medicare program and private health insurance. In particular, it provides information and analysis on healthcare coverage and access for the low-income population, with a special focus on Medicaid's

BioProducts

The Oncologist HD and Universal App

The Oncologist App for iPad is designed to help oncology, hematology and radiation professionals stay on the cutting edge of new medical treatments and technologies, encouraging better cancer patient care and practice management. Users can virtually flip through journal pages to access critical articles, as well as access rich multimedia options that enhance information visually and audibly, including embedded content not available in the traditional print edition. Both the HD and the universal app allow physicians to download podcasts of journal articles, as well as a library of content from conferences, symposia and roundtables of respected oncology experts. Future versions of The Oncologist App will integrate continuing medical education courses, making it easier for healthcare professionals to maintain educational requirements. The free app was last updated in July 2012.

AlphaMed Press, (919) 680-0011, theoncologist.alphamedpress.org

PICC-Line Placement Technology

The Sherlock 3CG* Tip Confirmation System (TCS) is Bard's next-generation, fully integrated magnetic tracking and ECG-based peripherally inserted central catheter (PICC) tip confirmation technology, which represents the next evolution of the Sherlock* II Tip Location System and the previously marketed Sapiens Tip Confirmation System. It is indicated for use as an alternative to chest X-ray and fluoroscopy for PICC tip placement confirmation in adult patients. Features include catheter tip tracking and ECG confirmation integrated on the same graphical display, static ECG baseline that provides comparative ECG waveform for interpretation of P-wave changes and to assist in maximum P-wave identification, dynamic ECG waveform to measure changes in P-wave morphology to position the catheter tip in proximity to the cavoatrial junction, a through-drape connection to maintain maximal barrier sterile field during placement, a probe and wireless remote to maintain sterility while interfacing with TCS, tip confirmation documentation to document the PICC location in the patient's chart or to store it on the Sherlock 3CG* TCS System, and AVA and INS guidelines for proper PICC placement.

Bard Systems, (800) 545-0890

Subcutaneous Immunoglobulin Needle Sets

The newly FDA-approved needle set, called neria multi for large-volume infusions, is designed for subcutaneous infusion of immunoglobulin indicated for primary immune deficiency disease patients. It has the benefit of a flexible finger grip for easy insertion, an adhesive with a window to view the site, and a pre-attached adhesive, excluding the need for extra tape/Tegaderm.

IntraPump, (866) 211-7867, www.neria.com/index.asp?pageid=H3513

3-D Medical Scanner

Engineers from the University of Illinois at Urbana-Champaign have created a new imaging tool for primary care physicians: a handheld scanner that enables them to image all the sites they commonly examine, and more, such as bacterial colonies in the middle ear in 3-D, or monitor the thickness and health of patients' retinas. The new handheld imaging device would give doctors a way to quantitatively monitor chronic conditions such as ear infections and possibly make more efficient and accurate referrals to specialists.

The device relies on optical coherence tomography (OCT), a visualization technology that is similar to ultrasound imaging, but uses light instead of sound to produce the images. The scanners include three basic components: a near-infrared light source and OCT system, a video camera to relay real-time images of surface features and scan locations, and a microelectromechanical systems (MEMS)-based scanner to direct the light. Near-infrared wavelengths of light penetrate deeper into human tissues than other wavelengths more readily absorbed by the body. By measuring the time it takes the light to bounce back from tissue microstructure, computer algorithms build a picture of the structure of tissue under examination.

UIUC physician and biomedical engineer Stephen Boppart and his team are hopeful that falling production costs combined with smaller, more compact designs will enable more physicians to take advantage of the scanners, and that they will become a common point-of-care tool. Boppart and an international team of collaborators recently received a \$5 million National Institutes of Health Bioengineering Research Partnership grant to further refine the device.

The Optical Society, (202) 416-1443, www.osa.org/en-us/about_osa/newsroom/newsreleases/2012/3-d_medical_scanner_new_handheld_imaging_device_to

BioDashboard

IVIG Reimbursement Calculator

Medicare Reimbursement Rates*

Rates are effective January 1, 2013 through March 31, 2013.

Product	Manufacturer	HCPCS	ASP +6% (per gram)
CARIMUNE NF	CSL Behring	J1566	\$69.47
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	\$69.89
GAMMAGARD LIQUID	Baxter BioScience	J1569	\$75.27
GAMMAGARD S/D	Baxter BioScience	J1566	\$69.47
GAMMAKED	Kedrion	J1561	\$76.46
GAMMAPLEX	Bio Products Laboratory	J1557	\$73.18
GAMUNEX-C	Grifols	J1561	\$76.46
OCTAGAM	Octapharma	J1568	\$63.20
PRIVIGEN	CSL Behring	J1459	\$71.14

* Hospital outpatient and physician office settings

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Indication	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: PIDD, MMN 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
OCTAGAM Liquid, 5%	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g	Octapharma
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

MMN Multifocal motor neuropathy
PIDD Primary immune deficiency disease

2012-2013 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 Intradermal	0.1 mL microinjection	Influenza virus vaccine, split virus, preservative free, for intradermal use	90654
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
FLUARIX	0.5 mL prefilled syringe		
FLUVIRIN	0.5 mL prefilled syringe		
FLUZONE	0.5 mL single-dose vial		
FLUZONE	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
FLUMIST	0.2 mL nasal spray	Influenza virus vaccine, live, for intranasal use, when administered to individuals 2-49 years of age	90660
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
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to individuals 3 years and older, for intramuscular use	Q2035
FLULAVAL			Q2036
FLUVIRIN			Q2037
FLUZONE			Q2038

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 ($\geq 5\%$) with intravenous use of GAMUNEX-C were headache, cough, injection site reaction, nausea, pharyngitis and urticaria. The most common adverse reactions ($\geq 5\%$) 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 $\geq 5\%$ of subjects) were headache, vomiting, fever, nausea, back pain and rash.
- **CIDP** – The most common adverse reactions during clinical trials (reported in $\geq 5\%$ 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 has proven efficacy and patient outcomes in CIDP, PI, and ITP*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, Grifols.

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.

i To get GAMUNEX-C call 1-888-MY GAMUNEX (694-2686)
USA Customer Service: 1-800-243-4153
www.gamunex-c.com

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