January 2014

BioSupply Trends

Special Focus: PLASMA

Quarterly

PLASMA THERAPIES

The Healing Power of Proteins

IG Product Differentiation and Reimbursement

Treating Cancer with Gene Therapy

Coagulation Factor Disorders: Types and Treatments

Update on Rheumatoid Arthritis

Thirty Years of IVIG Clinical Research — Page 50

Flublok®

Influenza vaccine

Pure Simple Effective

ACIP recommended for ages 18-49

Also recommended for those with egg allergies

To order Flublok, contact
FFF Enterprises: www.MyFluVaccine.com or
(800) 843-7477

Protein Sciences
CORPORATION

Reimbursement Codes
CPT code: 90673
Q code: Q2033

Flublok (Influenza Vaccine)
Sterile Solution for Intramuscular Injection
Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Flublok safely and effectively. See full prescribing information for Flublok available at www.Flublok.com.

INDICATIONS AND USAGE

Flublok is a vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine. Flublok is approved for use in persons 18 through 49 years of age.

DOSAGE AND ADMINISTRATION

A single 0.5 mL dose for intramuscular injection.

DOSAGE FORMS AND STRENGTHS

A sterile solution for injection supplied in 0.5mL single dose vials.

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

In adults 18 through 49 years of age, the most common (≥10%) injection-site reaction was pain (>37%); the most common (≥10%) solicited systemic adverse reactions were headache (>15%), fatigue (>15%) and myalgia (>11%).

To report SUSPECTED ADVERSE REACTIONS, contact Protein Sciences Corporation at 1-888-855-7871 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of Flublok have not been established in pregnant women, nursing mothers, children, or adults 50 years of age and older.
- A pregnancy registry is available for Flublok. Contact: Protein Sciences Corporation by calling 1-888-855-7871.

Issued: December 2012

Manufactured by:
Protein Sciences Corporation
1000 Research Parkway
Meriden, CT 06450
(203)686-0800 • www.proteinsciences.com

FB13017

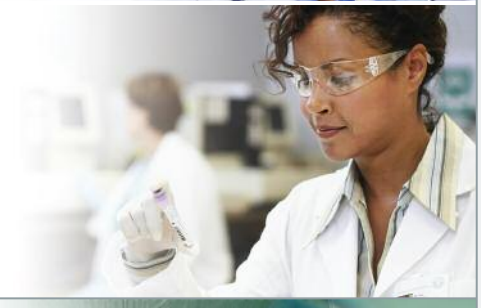
www.Flublok.com

BioSupply Trends Quarterly

January 2014

Features

Special Focus: Plasma



About BioSupply Trends Quarterly
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Human Plasma: Evolving Uses

SINCE THE ADVENT of randomized controlled clinical trials that came into widespread use in the 1970s, medicine has been an evolving discipline. Now, almost a half century later, virtually all medical therapeutic options are being questioned, evaluated and re-evaluated by researchers all across the world, and what we know about medicine is being altered one answer at a time. In this issue, we look at the answers we currently have about the use of human plasma therapies, as well as the expanding number of studies being conducted to both challenge old answers and provide us with new ones.

As you may recall, the 1970s was a turning point for one of the most well-known plasma therapies, coagulation factor, which was indicated for patients with bleeding disorders. Prior to the availability of coagulation factor therapies, many people with severe hemophilia, and some people with mild or moderate forms, died in childhood or early adulthood. Fortunately, as our article "A Review of Coagulation Factor Disorders" explores, coagulation factor therapies continue to improve the long-term outcome for people with the different types of hemophilia, as well as those with the most common bleeding disorder, von Willebrand disease. Unfortunately, the number of people diagnosed with bleeding disorders is predicted to remain constant, which is why researchers are continuing to study how coagulation factor therapies can be improved, as well as how other medical advances in the fields of biotechnology and gene therapy can possibly cure these disorders.

Another well-known plasma therapy, immune globulin (IG), was first used in the 1950s as a treatment for primary immunodeficiency disease, but it did not become commercially available until 1981. Now, 30-plus years later, IG is used to treat six FDA-approved diseases, as well as a host of non-FDA-approved diseases. But, much has changed between the IG products originally on the market and those that are available today. Not only are current products greatly improved in terms of composition, they have significantly fewer adverse reactions. Our article "Immune Globulin: Each Product Is Unique" takes a look at the key differences among today's products and how each must be best-suited to the characteristics of the patient receiving the treatment.

IG therapy is most certainly one of the most prized examples of how researchers are exploring the therapeutic options for plasma therapies. Today, there are dozens of U.S. and international clinical trials evaluating IG for hard-to-treat diseases — most notably, autoimmune disorders and inflammatory dysregulation. Our article "Thirty Years On, IVIG Clinical Research Keeps Rolling" examines "what's hot" in intravenous IG clinical research and how global research interest in IG has revealed how much we have yet to discover about its therapeutic potential.

To many patients, medicine appears to be a complete book of knowledge, but where medicine is practiced, it's clear that this book is ever changing and expanding. In this and every issue of *BioSupply Trends Quarterly*, we will continue to provide you with updates on these changes. As always, we hope you enjoy this issue of *BioSupply Trends Quarterly* and find the content educational and insightful. We welcome your comments.

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

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

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Track-and-Trace, Compounding Reform Bill Signed Into Law

The Drug Quality and Security Act (H.R. 3204) that provides uniform, nationwide standards for both pharmacy compounding and drug tracking was enacted into law in November. The bill came as a response to a report from the Government Accountability Office that confirmed legislation was needed to clarify the Food and Drug Administration's (FDA's) oversight of large-scale drug compounders. It also replaces the current patchwork of state drug tracing laws and establishes a nationwide track-and-trace pharmaceutical system.

The new law applies a uniform national standard to the oversight and inspection of compounding pharmacies that produce large volumes of custom pharmaceuticals so that they are regulated more like drug manufacturers. Specifically, pharmacies must register as "outsourcing facilities" and be subject to FDA regulation. They can compound drugs only from bulk ingredients that appear on a list compiled by the Health and Human Services Department. Drugs are required to be compounded under the direct oversight of a pharmacist, but facilities are not required to have a prescription to provide compounded drugs. The drugs sold in the previous six months must be reported every six months, and any serious adverse drug experiences must be reported within 15 days, plus facilities are required to conduct follow-up investigations and reporting. Facilities will be inspected by FDA according to a risk-based schedule, with companies paying a $15,000 annual fee to FDA to support these inspections (compounding manufacturers with under $1 million in gross revenue will pay a reduced fee). FDA may also publish the name, state location and specific information about drugs compounded by the facilities. Last, outsourcing facilities are exempt from certain requirements, including the national track-and-trace provisions established under the bill.

Under the track-and-trace provision, all members of the pharmaceutical distribution supply chain — manufacturers, wholesale distributors, pharmacies and repackagers — are required to keep detailed records of transactions made between them when drugs change hands. Specifically, they must transmit specific information about each drug upon each transfer, and they must maintain transaction statements and histories for a minimum of three years. For all transfers, a transaction history showing all prior transactions, beginning with the manufacturer, must be provided. The provision also requires all entities in the drug supply chain to promptly investigate whether a drug is contaminated, counterfeit or stolen, if requested by FDA. In addition, the law strengthens licensure requirements for wholesale distributors and specifically includes third-party logistics providers for the first time as part of the drug supply chain. Within four years of the bill's enactment, manufacturers will be required to include a "prescription drug product identifier," or nationwide drug serial number. By seven years after the bill's enactment, repackagers, wholesale distributors, pharmacies and other dispensers cannot receive drugs without such labels. Last, one of the goals of the bill is to develop a feasible pathway to unit-level tracing in 10 years.

FDA is developing a guidance process, a set of milestones and a public interface over the next two years in order to implement the law for 2015. ❖

CMS Makes Final Decision on PET Scan Coverage

In September, the Centers for Medicare & Medicaid Services (CMS) announced its final decision on a coverage policy that will limit patient access to beta-amyloid positron emission tomography (PET) imaging, a diagnostic tool for individuals with mild cognitive impairment. The policy will require Coverage with Evidence Development for dementia sufferers, meaning patients will need to undergo costly and lengthy clinical trials to get Medicare coverage for the scan.

In July, more than 1,200 Alzheimer's supporters urged CMS to provide coverage for the PET beta-amyloid imaging scan, which has the capability to more accurately diagnose those being evaluated for dementia spectrum disorder, including Alzheimer's disease. In addition to these benefits, the imaging technology can help researchers enhance design and enlistment of clinical trials for prospective dementia and Alzheimer's therapies. George Vradenburg, chairman of USAgainstAlzheimer's, said, "USAgainst Alzheimer's will continue to collaborate with other leaders in the field to educate CMS and other payers about the importance of thorough and meaningful coverage for patients across the entire dementia spectrum." ❖

FDA Awards Seven Grants to Stimulate Pediatric Medical Device Innovation

In September 2013, the U.S. Food and Drug Administration (FDA) awarded $3.5 million in grants to enhance the availability and development of medical devices for children. FDA's Office of Orphan Products Development presented the grants to seven pediatric device organizations, each with a team of specialists with expertise in delivering regulatory, business, scientific, engineering, legal and clinical services for children.

Children present a unique challenge to the medical device developer community because their body chemistry, stature and growth rate differ from child to child. Medical device legislation was passed by Congress in 2007 to help establish a continuous flow of funding for nonprofit institutions to help stimulate projects to promote the advancement of pediatric devices. This legislation was re-approved as part of the FDA Safety and Innovation Act of 2012.

Grant recipients intend to accomplish four goals: inspire creation and unite skilled individuals with innovative pediatric device ideas to prospective manufacturers; guide pediatric device projects through their development, including prototype design and marketing; join innovators and healthcare professionals with available federal and non-federal resources; and evaluate the scientific and medical merit of suggested pediatric projects and offer support and advice on industry growth, training, prototype development and post-marketing requirements.

This is the third time since 2009 that FDA has presented grants to pediatric medical device organizations. Each of the seven grant recipients will coordinate with FDA, device companies and the Eunice Kennedy Shriver National Institute of Child Health and Human Development to promote research and the advancement of any necessary applications for device clearance and approval. In addition, they will work with FDA to guide innovators through current laws and regulations to create safe and effective medical devices for children of all ages. ❖

"Champions" Help Consumers Understand New Insurance Marketplace

U.S. Health and Human Services Secretary Kathleen Sebelius recognized more than 900 Champions for Coverage organizations nationwide in September. These businesses have trained and certified volunteers from each state who will help Americans without affordable insurance to learn about their Health Insurance Marketplace options and help them enroll in a plan.

Champions for Coverage is composed of national and local hospitals, civic organizations, communities of faith, bloggers and community health centers. Volunteers from these organizations use print and digital materials provided by the Centers for Medicare & Medicaid Services to assist consumers through the enrollment process. They also assist consumers by posting information on their websites, providing health law information in their offices and hosting educational events.

To view the list of Champions for Coverage organizations, visit marketplace.cms.gov/help-us/champion.html. To join the growing list of Champions for Coverage, visit marketplace.cms.gov/help-us/champion-apply.html. ❖

Young Adults Needed to Make Health Law Successful

The success of the newly operational state health insurance exchanges depends heavily on insuring healthy, young adults to balance the risk of covering older, less healthy consumers. However, according to a recent survey from 2013, only 27 percent of young people are aware of the coverage options that went into effect on Oct. 1. "I think it's fair to say most young people will buy coverage if they consider it to be affordable and/or necessary, but until we see premiums, I think it's going to be really difficult for young people to assess whether this is affordable relative to all the other expenses they have," said Linda Rowings, chief compliance offer at United Benefit Advisors.

If healthy, young adults do not enroll in the new exchanges, health insurance premiums could increase substantially. ❖

WHAT YOU SHOULD KNOW ABOUT
HEMOLYTIC DISEASE OF THE NEWBORN (HDN)



QUESTIONS AND ANSWERS

What is hemolytic disease of the newborn (HDN)?

If your body has produced antibodies to fight the antigens on your baby's red blood cells, a blood disorder called hemolytic disease of the newborn (HDN)—sometimes called rhesus (Rh) disease—can result. It is important to know that your body's production of these antibodies does not necessarily lead to HDN. But if it does, the results can be life-threatening, manifesting as anemia, jaundice, heart or liver problems, or mental retardation. Before any preventative treatment had been developed, HDN affected 1% of babies in second pregnancies born to Rh negative women in England and Wales.

What can happen if I have a different Rh blood group than my baby?

Having a different Rh blood group than your baby is only a potential problem if you are Rh negative and your baby is Rh positive. If a small amount of your baby's blood mixes with yours during pregnancy, your immune system may perceive this difference in blood type as a threat, producing antibodies that fight against your baby's blood. This process is called *sensitization* or *alloimmunization*, and once your body has made these antibodies, they cannot be removed. Sensitization is unlikely to affect your first pregnancy, but instead becomes a problem in any subsequent pregnancy if your baby is Rh positive. This is because the process of producing antibodies takes time. The initial antibodies you produce in your first pregnancy (IgM) cannot cross the placenta. These IgM antibodies are replaced by IgG antibodies—which can cross the placenta and adversely affect future pregnancies.

What are anti-D (RhD immunoglobulin) injections and when are they recommended?

Anti-D injections are given to pregnant women who are Rh negative as a means of preventing antibodies from forming against the baby's red blood cells. Anti-D injections are recommended after potentially sensitizing events that could result in a fetal/maternal hemorrhage: invasive procedures (amniocentesis), abdominal trauma, and delivery (C-section or vaginal).

If a patient fails to receive prophylactic RhD immunoglobulin at 28 weeks, when should she receive the first dose?

The dose should be given as soon as possible after it is recognized that the dose was missed. In such a case the second dose should be delayed until 6 weeks after the first dose.

COOMBS TEST

The Coombs test detects Rh incompatibility between mother and fetus.

To detect HDN, the presence of maternal anti-Rh immunoglobulin G (IgG) must be identified. In vivo, these antibodies destroy Rh positive fetal red blood cells (RBCs), but in vitro, they do not lyse cells or even cause agglutination, making them difficult to identify. Therefore, the Coombs test is used. This test uses antibodies that bind to human anti-D antibodies.

Reactions to Rh_0(D) immune globulin (human) are infrequent in Rh_0(D)-negative individuals and consist primarily of slight soreness at the site of injection and slight temperature elevation. While sensitization to repeated injections of human immunoglobulin is extremely rare, it has occurred.

Please see adjacent page for brief summary of full prescribing information.

Hyper**RHO**® S/D Full Dose

Rh_O(D) Immune Globulin (Human)

Solvent/Detergent Treated

BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

FOR INTRAMUSCULAR INJECTION ONLY

INDICATIONS AND USAGE

Pregnancy and Other Obstetric Conditions

Rh_O(D) Immune Globulin (Human) — Hyper**RHO**® S/D Full Dose is recommended for the prevention of Rh hemolytic disease of the newborn by its administration to the Rh_O(D) negative mother within 72 hours after birth of an Rh_O(D) positive infant, providing the following criteria are met:

1. The mother must be Rh_O(D) negative and must not already be sensitized to the Rh_O(D) factor.
2. Her child must be Rh_O(D) positive, and should have a negative direct antiglobulin test (see PRECAUTIONS).

If Hyper**RHO** S/D Full Dose is administered antepartum, it is essential that the mother receive another dose of Hyper**RHO** S/D Full Dose after delivery of an Rh_O(D) positive infant.

If the father can be determined to be Rh_O(D) negative, Hyper**RHO** S/D Full Dose need not be given.

Hyper**RHO** S/D Full Dose should be administered within 72 hours to all nonimmunized Rh_O(D) negative women who have undergone spontaneous or induced abortion, following ruptured tubal pregnancy, amniocentesis or abdominal trauma unless the blood group of the fetus or the father is known to be Rh_O(D) negative. If the fetal blood group cannot be determined, one must assume that it is Rh_O(D) positive, and Hyper**RHO** S/D Full Dose should be administered to the mother.

Transfusion

Hyper**RHO** S/D Full Dose may be used to prevent isoimmunization in Rh_O(D) negative individuals who have been transfused with Rh_O(D) positive red blood cells or blood components containing red blood cells.

CONTRAINDICATIONS

None known.

WARNINGS

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

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

NEVER ADMINISTER HYPER**RHO** S/D FULL DOSE INTRAVENOUSLY. INJECT ONLY INTRAMUSCULARLY. NEVER ADMINISTER TO THE NEONATE.

Rh_O(D) Immune Globulin (Human) should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

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

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

PRECAUTIONS

General

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive D^u test result. If there is any doubt about the mother's Rh type, she should be given Rh_O(D) Immune Globulin (Human). A screening test to detect fetal red blood cells may be helpful in such cases.

If more than 15 mL of D-positive fetal red blood cells are present in the mother's circulation, more than a single dose of Hyper**RHO** S/D Full Dose is required. Failure to recognize this may result in the administration of an inadequate dose.

Although systemic reactions to human immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactic reactions.

Drug Interactions

Other antibodies in the Rh_O(D) Immune Globulin (Human) preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within 3 months after Rh_O(D) Immune Globulin (Human) administration.

Drug/Laboratory Interactions

Babies born of women given Rh_O(D) Immune Globulin (Human) antepartum may have a weakly positive direct antiglobulin test at birth.

Passively acquired anti-Rh_O(D) may be detected in maternal serum if antibody screening tests are performed subsequent to antepartum or postpartum administration of Rh_O(D) Immune Globulin (Human).

Pregnancy Category C

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

Pediatric Use

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

ADVERSE REACTIONS

Reactions to Rh_O(D) Immune Globulin (Human) are infrequent in Rh_O(D) negative individuals and consist primarily of slight soreness at the site of injection and slight temperature elevation. While sensitization to repeated injections of human immune globulin is extremely rare, it has occurred. Elevated bilirubin levels have been reported in some individuals receiving multiple doses of Rh_O(D) Immune Globulin (Human) following mismatched transfusions. This is believed to be due to a relatively rapid rate of foreign red cell destruction.

GRIFOLS

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Research Triangle Park, NC 27709 USA
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08941119-BS

Research

New CMS and ACA Deadlines in 2014 for Physicians

Physicians will need to be on the outlook for a number of deadlines in 2014 coming from the Centers for Medicare and Medicaid Services (CMS), as well as a result of the Affordable Care Act (ACA). The deadlines pertain to the areas of quality of care, electronic health records and coding.

On Jan. 1, stage 2 of the CMS meaningful use incentive program began for eligible providers (EPs) who treat Medicare and Medicaid patients. EPs have until Oct. 1 of this year to demonstrate meaningful use and must do so for only a three-month period. Once the stage 2 requirements are met, Medicare EPs will receive a payment of $12,000 in 2014, and Medicaid EPs will receive $21,250. EPs who do not meet the deadline face penalties from 1 percent to 2 percent in 2015.

Also on Jan. 1, states that comply with expanded access to Medicaid as called for by the ACA must extend Medicaid to children and adults with a family or individual income that is less than 133 percent of the federal poverty level. Under the program, Medicaid payments will be raised to 100 percent of Medicare reimbursements for doctors who take on these patients. However, the incentive payments stop at the end of 2014, so those doctors who didn't sign up for the program in 2013 should plan to enroll early in 2014.

The reporting deadline for physicians to qualify for a 0.5 percent bonus for their participation in the Physician Quality Reporting System (PQRS) is nearing. Only physicians who signed up for the PQRS by Oct. 18, 2013, are eligible to qualify for this bonus. Those who submit performance data through Medicare claims or their electronic health record systems must do so by Feb. 28. Those who submit data through a patient registry have until the end of March. Physicians who failed to sign up for the PQRS by Oct. 18, 2013, will pay a penalty consisting of a 1.5 percent reduction in Medicare reimbursement in 2015.

March 31 is the deadline for physicians who do not qualify for Medicare or Medicaid and for those who are self-employed or who are small business owners to purchase plans in the insurance exchanges for themselves, their families and their employees. Those who fail to sign up for coverage must pay a tax at the end of the year.

Oct. 1 is the deadline for physicians to be up to speed and in compliance with the ICD-10 coding system, which contains 68,000 diagnosis codes (about five times the number found in ICD-9).

Last, Jan. 1, 2015, is the deadline to meet the care criteria under CMS's Medicare Physician Fee Schedule, which will include cost and quality data in calculating payments for physicians. The new payment structure will emphasize value of care as opposed to volume of care, and physicians who do not meet the care criteria will be penalized. By 2017, this value-based payment modifier will be applied to all physicians who bill Medicare for services provided under the physician fee schedule. ❖

Source: Mescape Special Report, Dec. 11, 2013.

Vaccines

Menactra Vaccine May Be Safe During Pregnancy

A study conducted by researchers at the Centers for Disease Control and Prevention found that pregnant women can safely receive the meningococcal vaccine Menactra. While the vaccine is not routinely recommended during pregnancy, Dr. Yenlik Zheteyeva, who led the study, said "women can be inadvertently exposed to these vaccines while pregnant, and providers may consider using these vaccines in pregnant women at increased risk for meningococcal disease."

The study reviewed data from the Vaccine Adverse Event Reporting System on pregnant women and infants born to women who received the vaccine in pregnancy between 2005 and 2011. Of the 103 reports, 65 described an adverse event, and the remaining 38 were submitted only because of vaccine exposure during pregnancy. The most frequent adverse event was spontaneous abortion in 17 cases (16.5 percent), but investigators say these events are relatively common and occur in approximately 15 percent to 20 percent of all pregnancies. The most frequent non-pregnancy related events were urinary tract infections (3.9 percent) and fever with vomiting (2.9 percent), both of which also are common in pregnant women. There was one report of a major congenital anomaly (aqueductal stenosis and severe ventriculomegaly), but the resarchers say this finding "is not informative and no inferences can be made." There were no maternal or infant deaths reported.

Menactra was licensed for use in the U.S. in 2005, and data support the safety of the vaccine for non-pregnant individuals ages 11 to 55. Teens are the main group to receive Menactra, and in 2005, the pregnancy rate in teenage females was 70 per 1,000, according to statistics on the U.S. Department of Health and Human Services website. The study was reported on in the February 22 online issue of the *American Journal of Obstetrics and Gynecology*. ❖

Research

Fluzone High-Dose More Effective Than Standard Dose in Older Adults

Results from a large clinical trial of Sanofi Pasteur's Fluzone High-Dose showed that the influenza vaccine was 24.2 percent more effective against lab-confirmed flu than the traditional vaccine dose in adults 65 and older. The Phase III trial was conducted over the past two flu seasons (2011-2012, which was considered one of the mildest in the past several years, and 2012-2013, which was considered moderately severe) at 126 centers across the U.S. and Canada, enrolling approximately 32,000 seniors. Half of the patients received the high-dose vaccine and the other half were administered the standard-dose vaccine. There was no placebo group. The researchers routinely called participants to ask about flu-like symptoms, and the study subjects were also asked to report any symptoms. When symptoms were reported, medical teams obtained nasopharyngeal swabs. Safety findings were similar to earlier findings, which showed a slightly higher risk of local reactions but not of serious adverse events. Fluzone High-Dose was approved in 2009 for adults 65 and older and contains four times as much antigen as standard-dose flu vaccines. ❖

Research

New Method Developed for Forecasting Flu Outbreaks

A computer model for predicting flu outbreaks weeks in advance has been developed by researchers at Columbia University and the National Center for Atmospheric Research. The model incorporates techniques used in weather prediction to forecast flu outbreaks up to seven weeks in advance, raising the possibility of flu forecasts that might one day help guide such decisions about when to increase vaccine production, close schools, better staff hospitals, etc. "Flu forecasting has the potential to significantly improve our ability to prepare for and manage the seasonal flu outbreaks that strike each year," said Irene Eckstrand, a program director at the National Institutes of Health.

To develop the model's formula, researchers used data from the Google Flu Trends project, which estimates outbreaks based on the number of flu-related search queries in a given region, as well as findings from a previous study that found wintertime U.S. flu epidemics tended to occur following very dry weather.

A practical use of the model is likely at least a year away, according to Dr. John Sinnott, director of the University of South Florida's Health Division of Infectious Disease and International Medicine. The findings were reported on in the Nov. 28, 2012, edition of the *Proceedings of the National Academy of Sciences*. ❖

Vaccines

Universal Flu Vaccine Effective in Animals

In a recent study, researchers tested a new universal flu vaccine containing nanoparticles created using hemagglutinin (HA), one of the major antigenic proteins in a flu virus's coat, and ferritin, an iron-transporting protein that naturally forms spherical clusters. When injected, the nanoparticles induced levels of anti-flu antibodies 34 times higher in mice and 10 times higher in ferrets compared with a traditional vaccine. Gary Nabel, now at Sanofi, who led the work in his former lab at the National Institute of Allergy and Infectious Diseases (NIAID), believes the results are because the HA molecules are much less densely packed on the nanoparticles than those on a real virus, and are not hidden by other coat proteins. "The immune system gets a better look at them," he explains.

Created by NIAID team member Masaru Kanekiyo, the nanoparticles infused HA and ferritin in such a way that the complexes automatically assembled into a structure with a 24-piece ferritin core from which protruded eight three-piece HA spikes, mimicking the natural HA spikes in the flu virus coat. "We created an entirely new molecule that hasn't been made before," Nabel says. "What's cool is that the whole thing self-assembles." Under the microscope, the nanoparticles look like simple jacks with eight spikes jutting out of a central ball. They are manufactured in the lab without having to grow real viruses in eggs or cell cultures, and they require fewer updates because they induce the production of antibodies that neutralize a wider range of flu strains. They may even protect against strains of the flu that have not yet emerged.

The study was published on *Nature*'s website on May 22. ❖

Research

Study Shows Protective Properties of Flu Vaccines

Collaborating scientists from Nationwide Children's Hospital, Baylor Institute for Immunology Research and Mount Sinai School of Medicine have identified an important mechanism for stimulating protective immune responses following seasonal influenza vaccinations. While seasonal influenza vaccines protect 60 percent to 90 percent of healthy adults from the flu, the mechanisms providing that protection are still not well understood.

In the study, blood samples before and after influenza vaccination from three groups of healthy study participants were analyzed for antibody responses. The groups included two sets of adults, one receiving flu vaccines during the 2009-2010 winter and the other receiving vaccination during the 2011-2012 winter, and a group of children who received the flu vaccine during the 2010-2011 winter. Analyses showed that a temporary increase in a unique subset of helper T cells expressing the co-stimulator molecule ICOS adds to the immune response by helping B cells produce influenza-specific antibodies.

Results indicated that at day seven following the administration of a flu vaccine in all groups, stimulated T cells were evident, contributing to the development of the immune response. The T cells positively correlated with increased antibodies against each flu virus strain examined, with the exception in the children's group against the swine-origin H1N1 virus. "Given that seasonal influenza vaccines induce antibody responses mainly through boosting the recall response of the immune system, this lack of correlation might reflect the lack of H1N1 specific immunity in some children," explained study co-author Emilio Flano, PhD, a principal investigator in the Center for Vaccines and Immunity at Nationwide Children's and an associate professor of pediatrics at OSU College of Medicine.

The study was published in the March 13 edition of *Science Translational Medicine*, a journal of the American Association for the Advancement of Science. ❖

Did You Know?

William Pollack, a medical researcher who helped develop a vaccine that virtually eradicated a disease once responsible for 10,000 infant deaths a year in the United States, died on Nov. 3 in Yorba Linda, Calif., at age 87. The vaccine is a gamma globulin solution known generically as Rh immune globulin and currently by its brand name, RhoGAM.

— The New York Times, Nov. 12, 2013

Medicines

More than Half of Healthcare Providers Now Write e-Prescriptions

A new study shows that more than half of those who write prescriptions today do so electronically. In the study conducted by the Office of the National Coordinator for Health IT in Washington, D.C., researchers studied the rise in e-prescription use from December 2008 to December 2012 by examining data from Surescripts, an e-prescription network that serves more than 240 million patients nationwide through most chain, franchise and independent pharmacies. During that study period, the share of doctors, nurse practitioners and physician assistants who used e-prescriptions jumped from 7 percent to 54 percent (or, 47,000 to 398,000). The share of prescriptions written electronically rose from 4 percent to an estimated 45 percent over the same period, with 86 percent of prescribers using electronic health records. And, the share of pharmacies able to accept e-prescriptions rose as well. At the start of the study period, 70 percent, or 43,000 pharmacies, could accept electronic prescriptions, and by December 2012, 94 percent, or 59,000, were able to do so.

The study described changes in federal law that provided incentives for physicians and pharmacies to convert to e-prescriptions, as well as grants that helped rural communities close technological gaps. In 2008, only 61 percent of rural pharmacies could take e-prescriptions compared with 75 percent of urban pharmacies. By 2012, this gap had closed (93 percent of rural and 94 percent of urban pharmacies could take e-prescriptions). In 2003, Congress passed the Medicare Modernization Act, which was followed by federal regulations and changes to state laws in 2006 that allowed exchanges of electronic information. In 2008, Congress passed the Medicare Improvements for Patients and Providers Act, which provided incentives to Medicare providers to use e-prescriptions. ❖

Medicines

FDA Approves Obinutuzumab for CLL

The U.S. Food and Drug Administration (FDA) has approved obinutuzumab (Gazyva, Genentech) for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). The drug is indicated for use in combination with chlorambucil. It is the first drug with a "breakthrough therapy" designation to receive FDA approval, which means it has the potential to offer a substantial improvement over available therapies for patients with serious or life-threatening diseases.

In the randomized multicenter Phase III trial of 356 patients with previously untreated CLL, those who received obinutuzumab in combination with chlorambucil had significantly better median progression-free survival than those treated with chlorambucil alone (23 months vs. 11.1 months). The most common adverse effects in patients receiving obinutuzumab were infusion-related reactions, neutropenia, thrombocytopenia, anemia, musculoskeletal pain and pyrexia. The drug is approved with a boxed warning about hepatitis B virus reactivation, as well as the drug's risk of inducing progressive multifocal leukoencephalopathy. However, according to the FDA, these are known risks with other monoclonal antibodies in the class, and rare cases have been identified in participants in other trials of obinutuzumab. ❖

Research

Climates Associated with Seasonal Flu Epidemics

Two types of environmental conditions — cold-dry and humid-rainy — are associated with seasonal influenza epidemics, according to an epidemiological study led by researchers at the National Institutes of Health's Fogarty International Center. The study, published in *PLOS Pathogens*, presents a simple climate-based model that maps influenza activity globally and accounts for the diverse range of seasonal patterns observed across temperate, subtropical and tropical regions.

The researchers used a recently developed global database that provides information on influenza peaks from 1975 to 2008 for 78 sites worldwide, spanning a range of latitude between 1 and 60 degrees, with 39 percent of the sites located in the tropics. To ensure independent validation, they also used epidemiological data from nine countries participating in FluNet, the World Health Organization's global influenza surveillance program. The nine countries included Spain, Tunisia, Senegal, Philippines, Vietnam, Colombia, Paraguay, South Africa and Argentina, none of which was represented in the original 78-location database, and were chosen because each country provided several years of data.

They found that temperature and specific humidity were the best individual predictors of the months of maximum influenza activity, known as influenza peaks. Specifically, they discovered that in temperate regions, influenza was more common one month after periods of minimum specific humidity, which happen to coincide with months of lowest temperature. In contrast, sites that maintained high levels of specific humidity and temperature were generally characterized by influenza epidemics during the most humid and rainy months of the year. "Anecdotal evidence suggests that colder climates have winter flu, while warmer climates that experience major fluctuations in precipitation have flu epidemics during the rainy season, and the current study fits that pattern," said Cecile Viboud, PhD, who headed the study. "In contrast, the seasonality of influenza is less well-defined in locations with little variation in temperature and precipitation, and is a pattern that remains poorly understood. One hypothesis that is often used to explain tropical influenza activity is that people congregate indoors more frequently during the rainy season, increasing contact rates and disease transmission."

Laboratory experiments suggest that low specific humidity facilitates the airborne survival and transmission of the virus in temperate regions. Specific humidity is the ratio of water vapor to dry air in a particular body of air, while relative humidity (commonly used in weather forecasts) is the amount of water vapor in the air relative to its capacity to hold water vapor, and is primarily a function of temperature.

The findings could be used to improve existing current influenza transmission models, and could help target surveillance efforts and optimize the timing of seasonal vaccine delivery, according to Viboud. ❖

People and Places in the News

FDA DESIGNATIONS

The U.S. Food and Drug Administration has assigned a priority review designation to **Celgene International Sarl's** supplemental drug application for the use of Abraxane (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) in combination with gemcitabine for the first-line treatment of patients with advanced pancreatic cancer.

APPOINTMENTS

Steven Pearl has been appointed as vice president of quality management for Critical Process Filtration Inc., a vertically integrated manufacturer and supplier of premium process filtration products and services. In this newly created position, Pearl will be responsible for quality systems, new product validation, design control in development of new products and product quality assessments. Pearl has more than 25 years of experience in developing and validating high-quality membrane-based products for use by biopharmaceutical manufacturers.

CLINICAL TRIALS

Anthera Pharmaceuticals has initiated the BRIGHT-SC Phase II study of blisibimod, a novel inhibitor of B cell activating factor for the treatment of IgA nephropathy, a chronic autoimmune renal disease characterized by proteinuria and progression to end-stage renal disease. ❖

Research

Registry Launched for Hemophilia A Patients

Grifols has launched the SPIRIT (Study of Plasma-derived factor VIII/VWF in Immune toleRance Induction Therapy) registry for patients with hemophilia A. The registry will enroll U.S. patients with hemophilia A and inhibitors being treated with Grifols' plasma-derived factor VIII/VWF product, Alphanate (antihemophilic factor/von Willebrand factor complex [human]). According to the registry's lead investigator, Rebecca Kruse-Jarres, MD, of Tulane University, this observational study fills an important void. "There is not a lot of prospective data to help us understand how patients with inhibitors respond to treatment, especially as it relates to adherence and quality of life," she explains. "The data from the SPIRIT registry will give us more information to treat our patients and should complement the ongoing RESIST study." RESIST is an international immune tolerance induction study in patients who have already experienced a failure with a VWF-free FVIII concentrate. ❖

Vaccines

Potential Vaccine Could Be Effective in Newborns After Birth

Researchers at Boston Children's Hospital have identified a potent compound that activates immune responses in newborns' white blood cells substantially better than anything previously tested, and that could make vaccines effective right after birth. Due to newborns' underdeveloped immune systems, they don't respond to most vaccines, leaving them at high risk for infections like rotavirus, pertussis and pneumococcus. This potential vaccine would give physicians the ability to immunize infants at birth, rather than at 2 months of age, when most current vaccination series begin.

In their work, the researchers found that white blood cells have one receptor, the toll-like receptor 8 (TLR 8), that responds strongly to stimulation. They tested a panel of synthetic small-molecule compounds, known as benzazepines, that specifically target TLR 8. One benzazepine, VTX-294, produced a strong immune response in white blood cells from newborns (taken from cord blood samples), as well as whole blood from adults. The compound induced robust production of cytokines — chemicals that rally the immune response — and proved at least 10 times more potent than the best activator of TLR 8 known previously. It also triggered production of so-called co-stimulatory molecules that enhance immune responses. Even very low concentrations of VTX-294 strongly activated antigen-presenting cells, a type of white blood cell whose activation induces immune memory, which is key to effective responses to vaccines.

"This one receptor seems to lead to more adult-like responses — immediate, short-term responses that are more appropriate for fighting infections," said David Dowling, PhD, co-first author on the study. "We're excited about the benzazepines because they are already in the first clinical pipeline. That advances the potential for using them in a clinical study in human newborns once they have been proven safe in animal studies."

The research was published in the March 4 edition of *PLOS ONE*. ❖

Research

Immune System Therapy Shows Promise in Adults with Leukemia

A recent study of an experimental therapy that alters cancer patients' own immune cells to recognize an often-deadly form of leukemia has shrunk tumors and sent the cancer into remission in adults. While a similar immune system approach had previously shown promise in children with acute lymphoblastic leukemia (ALL), as well as in adults with a related form of leukemia, it is the first study to prove this therapy works in adults. ALL is more common in children but especially deadly when it occurs in adults. Current treatments cure an estimated 80 percent to 90 percent of children with ALL, but they are effective in only 30 percent or fewer of adult cases.

In the study, scientists extracted T cells from five patients ages 23, 56, 58, 59 and 66 with ALL. The T cells were then mixed with a harmless virus that inserted genes for a three-part molecule: one part that

trains T cells to recognize homing beacons on the leukemic cells, called CD19; one part that instructs T cells to kill any such cells they find; and one part that makes T cells survive longer than usual. The cells were then returned to the patients. Four of the patients' leukemia became undetectable in 18 to 59 days, and the fifth patient achieved remission eight days after treatment. According to Michel Sadelain, a doctor with Memorial Sloan-Kettering Cancer Center in New York who was co-leader of the study, the results were dramatic considering several of the patients had bone marrow "chock full of leukemia." The treatment, however, did come with complications. Two of the patients experienced a cytokine storm, which led to plummeting blood pressure and spiking fever. Both cases were managed with steroids.

The researchers have since successfully treated three additional patients, and they suspect the results might be better if treatment is begun earlier. They are raising funds for a larger study to be conducted at Sloan-Kettering, as well as other cancer centers. ❖

Research

Potential Chagas Vaccine Candidate Shows Efficacy

Researchers at the Sealy Center for Vaccine Development at the University of Texas Medical Branch (UTMB) at Galveston have developed a safe vaccine candidate for Chagas disease that is simple to produce and shows a greater than 90 percent protection rate against chronic infection in mice.

In the study, the researchers identified and tested potential Trypanosoma cruzi (also known as T. cruzi or Chagas disease) antigen candidates and delivery models to establish the safety and efficacy of a vaccine formulation known as TcVac3. Early experiments proved that delivery of the candidate antigens by a DNA-prime/protein boost approach, along with co-delivery of IL-12 and GM-CSF cytokine adjuvants meant to enhance the immune response, was effective in generating antibody and T cell responses. With two doses of the vaccine, the mice with TcVac3-induced antibodies exhibited 92 percent to 96 percent protection against chronic infection. The DNA/MVA approach increased the vaccine efficacy enough to omit one of the antigens and the adjuvants, making it a much simpler but still highly effective vaccine.

The study provides further evidence that a human Chagas vaccine is possible, a topic of debate among some who still believe that Chagas heart disease is the result of an autoimmune disorder. "This signals a scientific breakthrough — unprecedented vaccine efficacy for a common parasitic disease with no cure for chronic sufferers," said lead author Nisha Garg, PhD, professor of microbiology, immunology and pathology at UTMB. "If this vaccine proves practical, it could be approved in as few as five years for use in canines, which are reservoir hosts of the disease. As many as 20 percent of dogs may be infected in Texas alone, developing the same heart conditions as humans but mistaken by vets for heartworm."

The study was reported on in the March 26 edition of *PLOS ONE*. Future research will determine if the vaccine composition can be simplified even further. The resarchers already are conducting related trials in canines, and are working on preclinical trials of human patient samples, testing for immune response in patients who are already infected but not showing signs of the chronic disease. Results of both studies are anticipated in late 2013. ❖

Public Service

AARDA Creates Public Service Campaign for AD Patients

In response to a recent study that found roughly one-third of prescriptions for autoimmune disease (AD) patients go unfilled and a high level of physician mistrust exists among AD patients, the American Autoimmune Related Diseases Association (AARDA) has created a new multimedia public service campaign with tools designed to help patients make informed decisions about newly prescribed therapies and treatments.

"The 3-Second Adherence" campaign includes three components. The first is a free patient brochure with an innovative, newly developed prescription "Decision-Making Tree" that helps guide patients through the risk/benefit evaluation process. The second is a physician handbook with advice about how to get patients to comply or adhere to their course of treatment. And, the third component, designed for both doctors and patients, is an online video that demonstrates that when doctors take an extra three seconds to explain to patients why specific medicines are being prescribed for them, patient adherence increases dramatically.

Approximately 50 million Americans live with ADs, 75 percent of whom are women. AD is one of the top-10 leading causes of death of women under the age of 65. It encompasses more than 100 diseases, including psoriasis, Graves' disease, Sjogren's syndrome, multiple sclerosis, rheumatoid arthritis, Crohn's disease and lupus. And, it is responsible for more than $100 billion in direct healthcare costs annually.

"Most autoimmune diseases are chronic, and managing them on a day-to-day basis can be overwhelming, especially when patients have multiple diseases, which is often the case with ADs," said AARDA Executive Director Virginia T. Ladd, explaining that the study found that 30 percent of prescriptions are never filled and only 35 percent of newly diagnosed patients rely solely on their physician's advice when it comes to taking medication. ❖

Vaccine Update

Preclinical testing of a DNA synthetic vaccine by Inovio Pharmaceuticals Inc. for the virulent **Middle East respiratory syndrome (MERS)** coronavirus induced robust and durable immune responses, demonstrating the potential for a SynCon(R) DNA vaccine to prevent and treat this deadly virus. Since 2012, when the virus was first identified, 153 cases from nine Middle Eastern countries have been reported, and 42 percent of these cases have been fatal. MERS is similar to the SARS virus that infected 8,000 people several years ago. MERS differs from SARS in that it appears to be less contagious, but MERS is almost five times as fatal as SARS, which killed 10 percent of those infected. There is no vaccine or effective treatment for MERS.

Loyola University Medical Center is setting up a clinical trial for an experimental vaccine that trains a patient's immune system to fight **melanoma**. The process involves removing a batch of the immune system's killer T cells from the patient and modifying them in a lab. Two genes are inserted into the extracted cells so that they can recognize tumor cells as abnormal. The patient undergoes high-dose chemotherapy to kill most of the remaining T cells, to make room for the genetically modified T cells when they are put back in the patient. The modified T cells, it is hoped, will recognize the tumor cells as abnormal and then attack and kill them. In the trial, four doses will be tested, with the highest dose consisting of five billion genetically modified T cells. If the trial demonstrates the treatment is safe, scientists will proceed to the second part of the trial, which will determine if the treatment is effective.

The U.S. Food and Drug Administration has approved the first adjuvanted vaccine, Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, for the prevention of **H5N1 influenza** in people 18 years of age and older who are at increased risk of exposure to the H5N1 influenza virus. The vaccine is made using an egg-based manufacturing process and contains the adjuvant AS03, an oil-in-water emulsion. The H5N1 component and the AS03 adjuvant component are supplied in two separate vials, which must be combined prior to use. The vaccine is administered via intramuscular injection in two doses, 21 days apart. It is not intended for commercial availability. Instead, the U.S. Department of Health and Human Services has purchased the vaccine from the manufacturer, ID Biomedical Corp. of Quebec, Quebec City, Canada (a subsidiary of Glaxo SmithKline Biologicals), for inclusion within the National Stockpile for distribution by public health officials if needed. ❖

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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IMMUNE GLOBULIN

Each Product Is Unique

While all IG products are comparably effective, they also have relevant differences that determine their tolerability by patients.

By Ronale Tucker Rhodes, MS

The current availability of multiple immune globulin (IG) products gives providers many choices when prescribing this lifesaving therapy. With the approval of the latest IG product in December 2012, there are now 11 IG products that treat six U.S. Food and Drug Administration (FDA)-approved diseases (primary immunodeficiency disease, idiopathic thrombocytopenic purpura, multifocal motor neuropathy, chronic lymphocytic leukemia, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy), as well as a host of non-FDA-approved conditions.

The benefit of product choice, of course, is that it allows providers to match the best-suited product to the patient. And, this is extremely important because, while all products contain IgG (the most common protein in the body that helps ward off infections) and they all have comparable efficacy, they are not pharmaceutically equivalent. There are relevant differences between the current products on the market, considered third and fourth generation, that have evolved in terms of composition, resulting in decreased risk of infusion-related reactions and other adverse events. Product variations in sodium content, stabilizers, osmolality, osmolarity, IgA content, concentration and pH can affect the tolerability of a product for one patient versus another, based on both clinical conditions and comorbidities.[1,2]

Adverse effects of IG therapy have been greatly reduced in the last two decades; however, with the new generation of products, there are other serious adverse events that have been observed, including acute renal failure, aseptic meningitis, hemolysis and thrombosis. Some of these events can be attributed to either the size of the dose administered for specific indications, the rate of infusion, the differences between IG products or to characteristics of the patient receiving the treatment.[3]

When choosing an IG product based on the differences between each, the key factors a clinician considers are the patient's body type, weight, conditions presenting in addition to the one being treated with IG (such as diabetes, high blood pressure or other heart disease), whether they are pregnant or post-menopausal, other medications taken, kidney function, and if there is patient history of blood clots or migraines. This information is particularly important for dosing recommendation and premedication selection, and it helps clinicians tailor patient-specific suggestions for tolerating therapy.[4]

Following is a review of the key differences among the products' stabilizers, osmolality, IgA content and concentration, as well as a discussion of infusion rate and route of administration.

Stabilizers

When intravenous IG (IVIG) was originally approved by the FDA in 1981, it contained no stabilizers, and patients often experienced undesirable side effects such as fever, chills, fatigue and chest, hip, joint and back pain, which were believed to be due to the formation of immunoglobulin aggregates. To resolve this issue, stabilizers were added, primarily sugars such as sucrose, maltose, glucose and sorbitol, and in some cases, glycine and albumin.[5]

There are relevant differences between the current products on the market.

The specific stabilizer used can play an important role in a product's tolerability.[3] Today, most IG products are no longer stabilized with a sugar; however, a few still are, which can result in other adverse events. There is a strong association between renal failure and sucrose-containing products, rapid rates of infusion and diabetes. This is rare, and the cause of renal failure is unknown,[6] but it is believed that it could be due to the fact that sucrose has the highest osmotic activity of the stabilizers in IG products. In addition, since sucrose is metabolized by an enzyme, called sucrase, that is found only in the intestine, when administered intravenously, sucrose is eliminated unchanged in the urine, possibly resulting in osmotic nephrosis. And, while cautious use of IVIG is recommended in patients at increased risk for adverse renal events, including those with renal impairment, diabetes mellitus, age greater than 65 years, dehydration or hypovolemia, sepsis, paraproteinemia or concomitant use of nephrotoxic drugs, they are not contraindicated in patients with renal insufficiency.[5] In products stabilized with maltose, there is a possible interaction with strips that test for glucose in the blood. The maltose may cause an erroneous reading indicating glucose is high when it really isn't. However, most test strips have been modified to prevent these erroneous readings when maltose is present.[6]

Osmolality

Osmolality is the solute concentration contained in the IG solution; thus, the higher the osmolality, the higher the concentration of the IG solution.[6] Higher osmolality solutions, also known as hyperosmolar, are typically seen with older

lyophilized IVIG products. In contrast, today's fourth-generation products have a more physiologic osmolality comparable to that of individuals' blood because they have had amino acids glycine and L-proline added to them to help reduce the overall solute load, which can become elevated with sugars.[3]

Hyperosmolar solutions tend to cause more local venous irritation at the infusion site.[3] They also may be associated with an increased risk of thrombosis.[6] Dehydration also can cause the blood to become hyperosmolar, which is one of the reasons people receiving IG therapy are encouraged to drink a lot of water before, during and after the infusion.[6]

IgA Content

All IG products contain varying amounts of IgA (one of the five classes of antibodies found in the blood). IgA is not problematic for most people.[6] However, in patients who are IgA deficient, IgA can cause the formation of anti-IgA antibodies that can cause anaphylactoid reactions upon infusion of IVIG, which would result from the IgE development against IgA. While the risk of anaphylactoid reaction in IgA-deficient patients is anticipated, the incidence is low given the total number of reactions reported compared with the overall number of patients. In fact, screening for IgA deficiency prior to IVIG infusion is not routinely recommended.[3]

The amount of IgA in a given IG preparation may also influence the risk for common reactions that are milder such as fever, malaise, myalgia and headache.[3]

Osmolality is the solute concentration contained in the IG solution; thus, the higher the osmolality, the higher the concentration of the IG solution

Concentration

Today's IG products come in 5%, 10% and 20% solutions.[6] The solution percentage is the number of grams of IgG protein in an IG therapy solution. For instance, a 5% IG product

contains 5 grams of IgG protein per 100 mL of solution, a 10% IG product contains 10 grams of IgG protein per 100 mL of solution, etc. The highest-concentration 20% solution can only be infused subcutaneously. Three of the higher-concentration 10% products can be infused subcutaneously, while all of them can be infused intravenously. The lowest-concentration 5% products are approved only for intravenous infusion.

Most of today's products are available as a ready-to-use liquid formulation.[6] However, there are two products that are lyophilized and require reconstitution and pooling into an evacuated container for administration to the patient.[2]

Routes of Administration

IG can be administered intravenously through a vein (IVIG) approximately once every three to four weeks, or subcutaneously under the skin (SCIG) every other week, once weekly or twice weekly. SCIG is FDA-approved therapy for only primary immunodeficiency, although it has been prescribed to treat other conditions.[6]

Risk-assessment guidelines are important tools when dosing regimens and routes of administration are being considered. Guidelines include evaluation of patient history and physical examination, risk factors, comorbidities and tolerance to

appropriately manage potential serious and nonserious adverse events.[7]

SCIG is not appropriate for everyone. For those requiring IG for autoimmune disorders, the SCIG route of administration may not be possible due to the large volume of solution needed for a dose. However, for someone receiving a smaller dose, SCIG administration may be possible. Those with very thin skin don't tolerate SCIG as well as those with normal or thicker skin. And, very thin patients may not have enough fatty tissue in the space between the skin and the muscle to tolerate the SCIG infusion. Conversely, patients with very small veins or who have difficulty getting an IV started may be great candidates for SCIG.[6]

In the past several years, SCIG has become an alternative method of administration of IVIG because of its many advantages. For one, SCIG results in a reduction in anaphylactoid reactions due to its slower absorption from the subcutaneous tissue into the systemic circulation. SCIG also eliminates the need for vascular access, stabilizes immune globulin levels and increases patient autonomy. And, notably, it has been used by patients with IgA deficiency with antibodies against IgA without inducing hypersensitive reactions. There is, however, an increased incidence of local reactions such as swelling and redness at the site of infusion.[3]

Risk-assessment guidelines are important tools when dosing regimens and routes of administration are being considered.

Infusion Rates

Each patient has a maximum tolerated rate of infusion based on his or her risk factors and infusion-related reactions.[7] For all patients, and this is essential for those just beginning therapy, IVIG should be administered slowly initially and titrated as tolerated.[1] In general, primary immunodeficiency patients can be administered IVIG in one day approximately once a month (the half-life of IVIG is approximately 30 to 40 days), and they can be administered SCIG in one day over a matter of hours once or twice a week, or every two weeks as specified in the product labeling.[7] On the other hand, patients with autoimmune diseases are generally administered larger doses of IVIG that, in some instances, may be divided into daily infusions over two to five days.[3]

Slower rates of infusion have been linked to a reduced risk of side effects, including common reactions, acute renal failure, aseptic meningitis and thromboembolic complications. One of the most commonly reported side effects of IG therapy is headache, which has been found to increase with larger doses infused over a shorter period of time. Cases of aseptic meningitis are rare, but when it occurs, it requires discontinuation of IG treatment, and the symptoms typically stop after three to five days. Several causes for this have been proposed, including hyperviscosity that may be the result of rapid infusions of high doses into a volume-depleted hyperviscous bloodstream.[3]

Stopping an infusion at the first sign of reaction tends to be the best way to manage it. After symptoms abate, most patients tolerate continuing the infusion at a slower rate.[8]

Highly Improved and Tolerated Products

With advances in manufacturing processes, today's IG products are safer than ever before. However, every IG product has different pharmaceutical characteristics, and there is even variation from batch to batch of each product. It's these differences that can influence patient tolerability. But with careful patient screening and understanding of the inherent differences in the products, clinicians can ensure that the most appropriate product is prescribed to the patient. ❖

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

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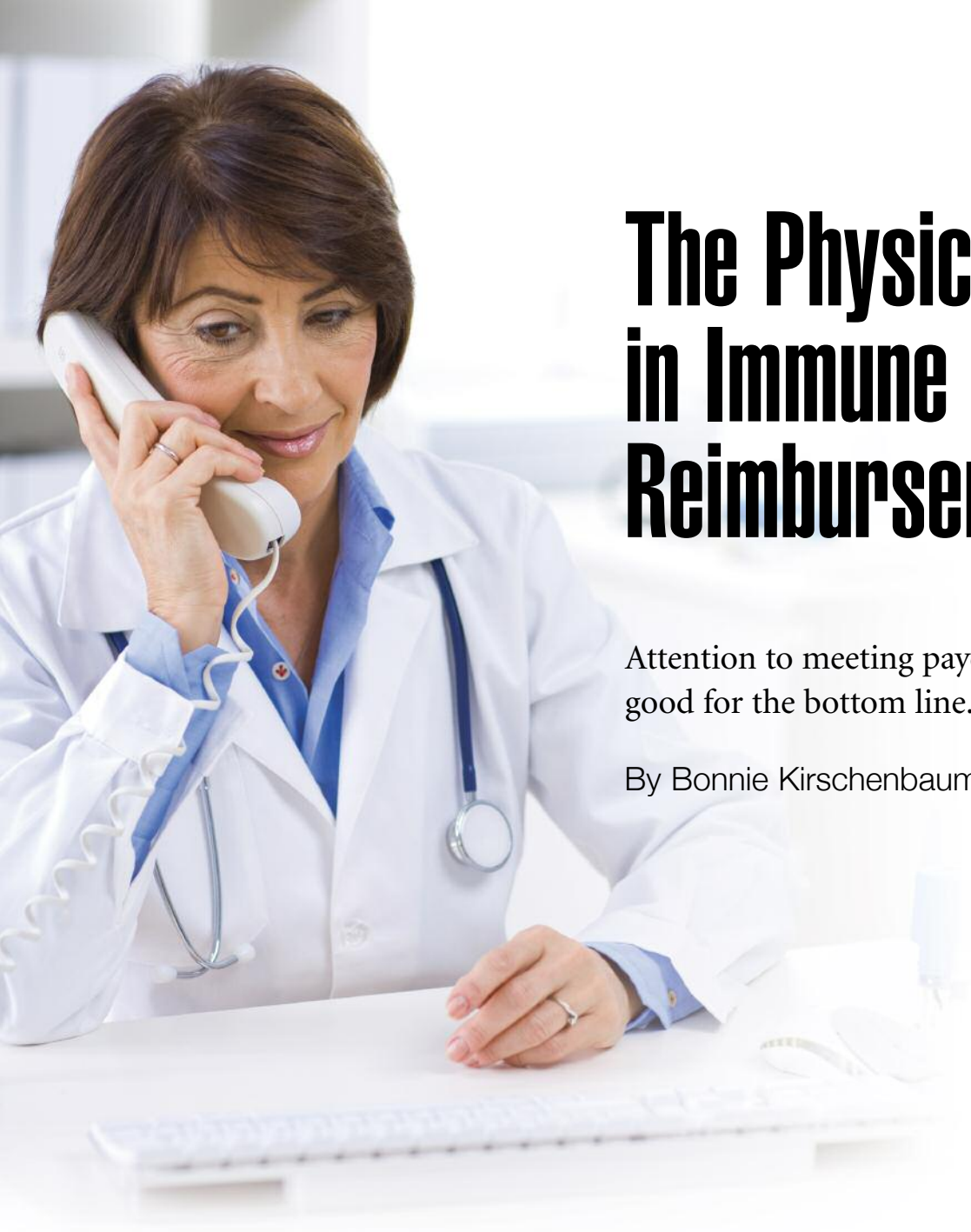

The Physician's Role in Immune Globulin Reimbursement

Attention to meeting payer requirements is good for the bottom line.

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

There's no question that healthcare professionals have an overflowing basket of tasks and important issues to tackle, as well as a myriad of infrastructure problems to solve. But, ensuring a healthy revenue stream is a priority, too. And, when it comes to expensive medications such as immune globulin (IG), a healthy revenue stream relies upon clinicians caring about reimbursement. Reimbursement is everyone's responsibility. Knowing and adapting to the nuances of how to be reimbursed for a product often prevents having to challenge payment denials.

Data drive decisions, and data are submitted to the payer making decisions about reimbursement regardless of whether the payer is Medicare, Medicaid or the private sector. Submitting data can be a challenge for clinicians with the workforce and budget changes that are the result of the myriad of new payment models that healthcare insurance reform has spawned. But, clinicians are expected to be players, not barriers, to implementing these changes. After all, reimbursement is what pays for the care that clinicians' facilities offer.

Discussed here are some areas that may be overlooked when it comes to reimbursement for IG under Medicare, the model that third-party payers and Medicaid often follow.

A Quick Reimbursement Review

Whether patients are considered inpatients or outpatients has nothing to do with where in a hospital facility patients are located or are being treated, but everything to do with their

admission status. Anyone not admitted to the hospital as an inpatient is an outpatient, including observation patients.

Inpatients fall under the inpatient prospective payment system (IPPS) based on the Centers for Medicare and Medicaid Services (CMS) Medicare Severity Diagnosis Related Groups (MS-DRG) model, and with few exceptions, it has no provision for separate reimbursement for medications, biologics or immunologic agents. The MS-DRG model is the quintessential model of bundled payment under which facilities are paid a fixed amount based on an aggregate of all detailed information provided to Medicare. However, facilities are still required to line item each bill because that data is in part what determines reimbursement. Failure to provide accurate data is interpreted by Medicare as a product not being used, which subsequently results in artificially low reimbursement to facilities.

Outpatients fall into the outpatient prospective payment system (OPPS), which has provisions for separate reimbursement for some medications, biologics or immunologic agents. It also has a model of bundled or packaged payment for drugs under $90 per day in 2014 (proposed) with fixed amounts paid to facilities that are based on an aggregate of all detailed information provided to Medicare. Again, not providing accurate data results in artificially low reimbursement.

Billing for drugs, biologics and immunologics is based on billing units, with the actual dose administered being converted into the appropriate number of billing units. Several years ago, CMS implemented the concept of billing units rather than vial sizes when structuring reimbursement. Both Medicare and Medicaid use billing unit codes, although not necessarily the same ones, and implementation of this concept continues to plague facilities. Billing unit tables are not static, so vigilance is required to ensure that the correct billing units are matched to the correct Healthcare Common Procedure Coding System (HCPCS) billing codes. Failure to do so results in significant overcharging or undercharging, and the resulting complications, especially for very expensive medications such as IG, are a natural target for audit!

The Role of MACs

CMS has geographically assigned Medicare administrative contractors (MACs) to serve as intermediaries between healthcare facilities and CMS. All financial transactions are submitted by healthcare facilities to MACs to process them for payment. There are subtle differences between how each MAC chooses to operate such as the required documentation and a variety of other issues. Therefore, it's imperative that facilities know who the MAC is for their region and that they get onto their MAC's e-distribution mailing list for updates.

Table 1. Prior Approval vs. NCDs and LCDs

	Prior Approval (Payer)	NCDs and LCDs
Applies to:	Third-party carriers (possibly Medicaid)	Medicare (possibly Medicaid)
Need patient's payer status before prescribing?	Yes	Yes
Should drug be tagged in CPOE?	Yes	Yes
Link to actual rule needed?	Yes	Yes
Rule requirements:	Ask permission first before drug administration	Understand and follow requirements; document completely and thoroughly; code correctly as required
Payment:	Only if permission is given first	Determined after the fact and may be denied if all rules not followed; predeterminations possible

When processing claims, MACs determine if all program requirements for coverage are met (e.g., whether the charges are reasonable and necessary to treat the beneficiary's condition or whether they're excluded from payment). This is often determined by local coverage determinations (LCDs), but also by national coverage determinations (NCDs), which apply to all geographies. The key is knowing the requirements upfront rather than having to fight them after the fact. It's a concept similar to prior authorization used by commercial payers.

A dilemma often arises when the literature supports treatment with drugs, biologics and immunologics for a non-U.S. Food and Drug Administration (FDA)-approved indication (known as an off-label indication). The fact that it's off-label may be sufficient grounds for a MAC to deny payment. This is certainly the case for IG products. Close review of each set of labelled indications reveals numerous differences between products, and they must be taken into consideration before products are ordered. Officially accepted compendia can be used to support an off-label decision, but clinicians should be aware of what they are. Patient and billing assistance programs offered by several of the pharmaceutical companies also may be helpful in providing support in attempting to overturn denials.

Clinicians often struggle with understanding and accepting that payer pre-approval is required for their clinical decisions, and they often perceive the task of gaining pre-approval as arduous and that it should be left to others. On the other hand, payers view this as documentation of data needed to ensure that the clinical decision is a reasonable and necessary one that contributes to the data pool that drives clinical decision support and evidence-based medicine. Table 1 compares prior authorizations required by third-party payers and CMS for LCDs and NCDs.

Electronic health records and the use of computerized physician order entries (CPOEs) with appropriately built code sets and links can streamline this process. Nevertheless, emphasis must be placed on understanding what's required before a product is ordered, and then completing and documenting the steps. Appeals of payment denials have little chance of success if this logic isn't followed. Documentation, tests or other required steps can't be done after the fact.

Understanding the Codes

Coding is the language that describes what treatment was performed and what drugs, biologics or immunologics were used. It is the operational link between coverage and payment. However, any payer at any time can decide it is not going to pay a claim.

• ICD-9 codes are currently used by hospitals to designate disease types. However, these codes will be replaced by ICD-10 codes in October 2014. Because of the increased complexity and specificity of ICD-10 codes, clinicians need to data mine

Table 2. Brand-Name Specific HCPCS Codes

HCPCS Code	Short Description	CMS Billing Unit
J1459	Inj IVIG privigen 500 mg	500 mg
J1460	Gamma globulin 1 cc inj	1 cc
J1557	Gammaplex injection	500 mg
J1559	Hizentra injection	100 mg
J1560	Gamma globulin > 10 cc inj	10 cc
J1561	Gamunex-C/Gammaked	500 mg
J1566	Immune globulin, powder	500 mg
J1568	Octagam injection	500 mg
J1569	Gammagard liquid injection	500 mg
J1571	Hepagam b im injection	0.5 mL
J1572	Flebogamma injection	500 mg
J1573	Hepagam b intravenous, inj	0.5 mL

• Most HCPCS codes are listed generically, but a few are unique to the brand name, and it is most likely this is the way biosimilars will be paid for.
•• All non-lyophilized intravenous immune globulin products have unique HCPCS codes.

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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: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including Privigen. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of human immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products that contain sucrose. Privigen does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer Privigen at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

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 hyperprolinemia, and in IgA-deficient patients with antibodies to IgA, who have had hypersensitivity reactions. Patients with IgA deficiency and antibodies to IgA are at greater risk of severe hypersensitivity and anaphylactic reactions.

In patients at risk for developing acute renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine; discontinue if renal function deteriorates. Ensure that patients with preexisting renal insufficiency or otherwise predisposed are not volume-depleted and administer Privigen at the minimum rate of infusion practicable.

Thrombosis might occur with Privigen, even in the absence of known risk factors. Patients could also experience hyperproteinemia, increased serum viscosity, or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur—more frequently with high doses (2 g/kg) and/or rapid infusion.

Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to treatment. Risk factors include non-O blood group, underlying inflammation, and high doses. Closely monitor patients for hemolysis and hemolytic anemia. Consider the 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 common adverse reactions observed in >5% of subjects were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness. Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature.

In clinical studies of patients being treated with Privigen for chronic ITP, the most common adverse reactions seen in >5% of subjects were headache, elevated body temperature, positive DAT, anemia, nausea, epistaxis, vomiting, increases in conjugated and unconjugated bilirubin, decreased hematocrit, and increased blood lactate dehydrogenase. A serious adverse reaction was aseptic meningitis syndrome (AMS).

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing. Use in pregnant women only if clearly needed. In patients over 65 or in any patient at risk of developing renal insufficiency, do not exceed recommended dose and infuse Privigen at the minimum rate practicable.

Please see brief summary of prescribing information for Privigen, including boxed warning, on adjacent page.

1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA
www.CSLBehring-us.com **www.Privigen.com**
PVG13-11-0038 12/2013

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

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

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-0 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 Privigen 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 Privigen (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 Privigen, occurred in one subject, and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative 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 Privigen 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 Privigen 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 Privigen 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 Privigen 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 Privigen. 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 Privigen. Three subjects experienced AEs that were considered to be at least possibly related to Privigen: 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 10^9/L or less received a total of 2 g/kg dose of Privigen 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 Privigen 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 Privigen, 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 Privigen.

One subject withdrew from the study due to gingival bleeding that was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention; 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 Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

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

6.2 Postmarketing Experience

Because 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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to determine what they are not currently documenting and receive very focused training.

• Current procedural terminology (CPT) codes are descriptive and identifying terms created by the American Medical Association and its specialty organizations for reporting medical services, procedures and lab tests that provide a uniform language describing medical, surgical and diagnostic services.

• HCPCS codes describe products. However, the fact that a drug, device, procedure or service has an HCPCS code and a payment rate under OPPS does not imply coverage by Medicare. Instead, it indicates only how the product, procedure or service may be paid if covered. Although most HCPCS codes are listed generically, beware that there are several brand-specific codes, too, and IG products are on that list (Table 2).

Understanding ASP Drug Pricing Files

CMS reimburses based on average sales price (ASP) and publishes a quarterly updated ASP drug pricing file in three formats. This file provides links to the actual listing of reimbursable Medicare Part B drugs and the amounts that will be

Getting in the Information Loop: Available Resources

1. Refresh your understanding of Medicare reimbursement with detailed information from Medicare reference manuals. These can be found at www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c17.pdf and www.cms.gov/Regulations-and-guidance/Guidance/Manuals/downloads/bp102c15.pdf.

2. Know your Medicare carrier or Part A/B MAC and how to contact them. There are subtle differences between carriers. Hint: Don't depend on a recommendation from a colleague covered by a different MAC. For an interactive map with toll-free MAC numbers, go to www.cms.gov/Research-Statistics-Data-and-Systems/Monitoring-Programs/provider-compliance-interactive-map/index.html.

3. Know where to find the list of medications with National Coverage Determinations (NCDs) and what these are. Use the link at www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx.

4. Know where to find the list of medications that have Local Coverage Determinations (LCDs) and what these are. Use the link to your local MAC and search their listed LCD section.

5. Know where to locate HCPCS codes. Look at long descriptions in the HCPCS tables to be clear about product descriptions; truncated short descriptions may be insufficient. Find the alphanumeric HCPCS sortable code listings at www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Alpha-Numeric-HCPCS.html, www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/HCPCS_Quarterly_Update.html and www.cms.gov/medhcpcsgeninfo.

6. Know what reimbursement rates for products are going to be, and confirm that the billing units you're using are correct. Use updated quarterly Medicare Part B Drug ASP tables available in three formats, one of which lists all NDC numbers associated with a particular HCPCS code, as well as the maximum number of billing units for that product. These can be found at www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2013ASPFiles.html and www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html?redirect=/mcrpartbdrugavgsalesprice.

7. Build an e-library, and add Centers for Medicare & Medicaid Services *MLN Matters* articles that refer to medications. These are vital to understanding actions you need to take to ensure reimbursement when it's available. If you don't ask for it correctly, you definitely won't be getting the correct amount! Past issues are easily retrieved. Note that past decisions may continue for several years and just be updated for reference purposes, so it's essential to get the complete picture. *MLN Matters* articles can be found at the CMS Medicare Learning Network at www.cms.hhs.gov/MLNProducts/downloads. Articles prior to June 2007 can be accessed in the archives at list.nih.gov/cgi-bin/wa.exe?A0=MLNMATTERS-L. Also, put yourself on the mailing list to keep current, and search back issues to establish a baseline; older or original announcements still prevail if nothing has changed. Search through the entire document because several issues may be covered in one publication. Put *MLN Matters* number MM8338 released June 7, 2013, and effective July 1, 2013, at the top of your list. The section on Billing for Drugs, Biologicals and Radiopharmaceuticals contains a wealth of information on drugs and biologicals with payments based on ASP.

reimbursed, as well as a reminder of the billing units for each drug code, the NDCs and the total billing units in each vial per NDC. ASP is calculated based on sales data from the manufacturer, not from the distributor. Not surprisingly, reimbursement for some drugs goes up, and for other drugs, it goes down. This can be a result of a number of competitive market factors: multiple manufacturers, alternative therapies, new products, recent generic entrants or market shifts to lower-priced products, as well as the weighting given to the package sizes sold.

Injectable Patient Assistance Drugs vs. White Bagged Drugs

There is little difference between injectable patient assistance drugs and white bagged drugs. In both cases, the drugs are sent to the physician office or pharmacy by a distributor, manufacturer or specialty pharmacy at no cost to the physician or pharmacy.

White bagging is the practice of having patient-specific medications or supplies delivered directly to the practice setting (outpatient infusion center, physician office, hospital) for use by a specific patient. The practice arose due to the requirements of some insurance carriers mandating the use of specialty pharmacy, manufacturer-supported patient assistance programs and/or FDA-assigned risk evaluation and mitigation strategy (REMS) programs.

Because the medications may be prepaid or complimentary, no billing for these products/supplies transpires. However, billing for the clinic visit where the drugs are administered and for the drug administration itself still brings income to facilities. Medicare has specific requirements for how this transpires, so it is essential for facilities to follow the guidelines determined by their MAC. Essentially, the drug is billed at a zero charge to indicate that it was administered, which allows the drug administration fee to be processed.

Getting Ready for 2014

Recently, proposed OPPS rules covering Medicare outpatient reimbursement were published, comments were reviewed, and final rules are to be published in early January. Following are some of the proposed rules affecting IG reimbursement.

New drugs not yet assigned a unique HCPCS code. An injectable drug first coming to market that has been given pass-through status but does not yet have an HCPCS code is paid for at 95 percent of average wholesale price using code C9399, unclassified drugs or biologicals, along with the NDC number of the product being administered. This is proposed to remain for 2014 to cover new entries into the market.

New pass-through drugs with HCPCS codes. If the manufacturer has diligently worked toward it, the new product may have an HCPCS code when FDA gives its approval. If so, it must be used. It is paid at wholesale average cost plus 6 percent until the ASP is available, at which time it is paid at ASP plus 6 percent. Pass-through status is time-limited, usually two to three years. This also is proposed to remain for 2014. The lists of products gaining and losing pass-through status for 2014 (proposed) have been published. Only one IG product is on the list: injection, immune globulin (Bivigam), 500 mg, HCPCS code C9130, status indicator G, APC 9130. And, one product lost this status: injection, immune globulin (Flebogamma/Flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg, 2014 HCPCS code J1572, status indicator K, APC 0947.

Specified covered outpatient drugs (SCODs) costing more than $90 per day. The majority of drugs are reimbursed in this category, which is where most drugs land once their pass-through status expires and where the cost per day of the product is assessed each year. Proposed for 2014 is that only drugs costing more than $90 per day will be separately reimbursed at a proposed rate of ASP plus 6 percent both in the physician office setting and by OPPS. This is how most IG products are paid for.

Lower-cost packaged products costing less than $90 per day. There is no separate reimbursement for these products. Rather, payment for them is included in the bundled payment for the specific procedure/visit for which they were used. However, if administered as infusions, payment for drug administration is available separately from the bundle.

Getting Reimbursed

To maintain a healthy revenue stream, clinicians must remain attuned to the nuances of reimbursement, as well as anticipate the increasing complexity and specificity the process will require. Increasingly, data analytics is driving decisions, and physicians are the ones contributing the data with every transaction their practice submits. ❖

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Source

Federal Register, Vol. 78, No. 139, July 19, 2013, Proposed Rules. Table 19: Proposed Drugs and Biologicals with Expiring Pass-Through Status 12.31.2013 (page 43599) and Table 20: Proposed Drugs & Biologicals with Pass-Through Status in CY 2014 (page 43600). Accessed at www.gpo.gov/fdsys/pkg/FR-2013-07-19/pdf/2013-16555.pdf.

A Review of Coagulation Factor Disorders

By Amy Ehlers, BS, PharmD, BCPS

Until better treatments or a cure can be found, coagulation factor replacement therapies continue to improve the long-term outcome for people with bleeding disorders.

Coagulation, or clotting, factors are the necessary proteins that allow the body to form a blood clot. There are 13 different types of clotting factors in the blood, each designated by Roman numerals I through XIII, that work both dependently and independently of each other in what is known as the clotting cascade (Figure 1).

When there is an injury or damage to an area of the body causing bleeding, several things begin to happen almost immediately. The affected blood vessels begin to contract in an effort to slow the blood flow to the area. Platelets begin to stick to the injured space and become "activated" to attract other platelets to the area. Through a process referred to as aggregation and adhesion, the platelets begin to form a plug in the blood vessel hole. It is on the surface of these activated platelets where the clotting cascade occurs and works to form a fibrin clot that will cause hemostasis.

In the event that any one of these factors or components is missing, present in lower than normal levels, or does not work properly, an individual may take longer to stop bleeding and would be diagnosed with a coagulation disorder. There are two types of coagulation factor disorders — hemophilia and von Willebrand disease — that are treated with several different factor replacement products.

Hemophilia

Hemophilia occurs when a person has missing or low levels of FVIII, FIX or, in extremely rare cases, FVII or FXI. It is usually an inherited disease that affects mostly males, although it may occur in people with no family history and also in women. According to the Centers for Disease Control and Prevention (CDC), hemophilia affects one in 5,000 male births, and approximately 400 babies are born with hemophilia each year. Those with hemophilia may experience bruises or bleeds from injuries, or bleeds may be spontaneous events. These bleeding episodes may occur internally in joints, muscles, soft tissues or organs. Untreated or repeated bleeds can cause permanent damage to these areas over time. If the bleeding is uncontrolled or occurs in a vital organ such as the brain, death may occur.

The type of hemophilia a person is diagnosed with is based on the specific factor deficiency that is present and may be further classified by the amount of that clotting factor that is present in the blood. In an individual with normal levels of FVIII and FIX clotting factors, this is 50 percent to 150 percent (Table 1).

While there is no cure for hemophilia at this time, it may be managed with replacing the factor deficiency either prophylactically to prevent bleeding or on demand to treat the bleed. All factor replacement products are given intravenously and, in many cases, by the patients themselves (see Table 2 for a list of factor coagulation products available in the U.S.). Prophylactic therapy is the routine administration of factor one to three times a week. The dose and frequency is based on several patient-specific factors such as age, weight, severity and activity level. The goal of prophylactic factoring is to prevent bleeding episodes from occurring, therefore avoiding many of the associated complications. On-demand or as-needed dosing may be used by all patients to treat an active bleed, or it may be used prior to an event (e.g., medical procedure) that will most likely result in a bleed. An active bleed may require infusions for multiple days or even more than one dose per day to treat.

FVIII deficiency, also known as hemophilia A or classic hemophilia, is the most common type of hemophilia as it accounts for 80 percent of all diagnosed patients. FVIII products may be plasma-derived or recombinant. While there are many different FVIII replacement products available, each offering unique characteristics in terms of manufacturing process, diluent volume, accompanying supplies and storage requirements, all may be used for patients with FVIII deficiency and need to be reconstituted prior to administration.

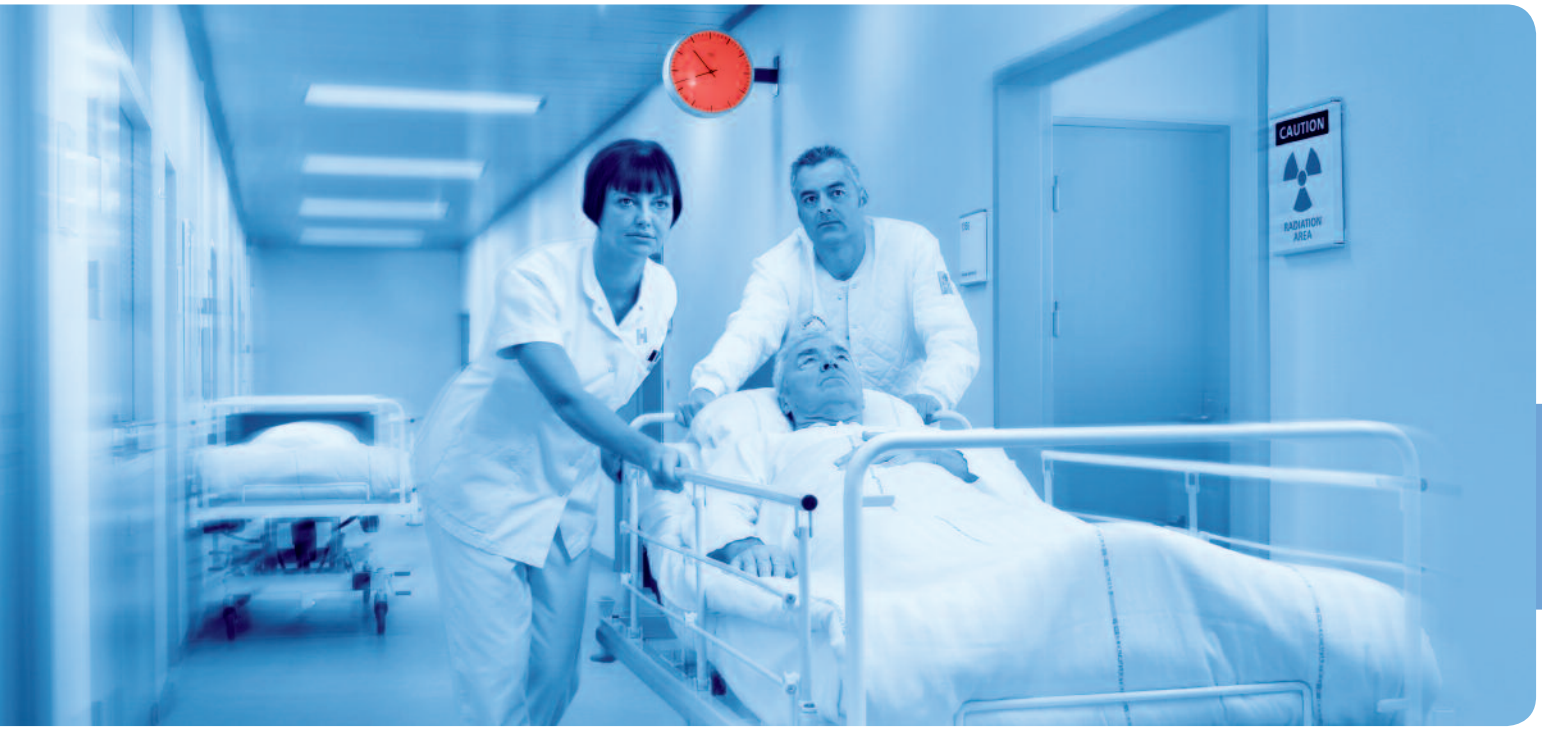
Factor VIII deficiency, also known as hemophilia A or classic hemophilia, is the most common type of hemophilia as it accounts for 80 percent of all diagnosed patients.

FIX deficiency, also known as hemophilia B or Christmas disease, is much less common than FVIII deficiency, comprising 15 percent of hemophilia patients. FIX products are also available as plasma-derived or recombinant.

It is important to note that patients with FVIII or FIX deficiency must be treated with the specific factor they are lacking for the treatment to be successful. This is because FVIII and FIX are independent clotting factors in the clotting cascade, which means that the action of one is not dependent on the action of the other.

While individuals with FVII deficiency are rare, a FVII replacement product may be used to treat it, as well as FVIII or FIX bleeding disorders. The reason for the latter is because

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



Indications and Usage

NovoSeven® RT (Coagulation Factor VIIa [Recombinant]) 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

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 0.3% of bleeding episodes treated, with the incidence in acquired hemophilia of 4% and in hemophilia patients of 0.2% 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.

novo nordisk®

NovoSeven® RT is the only bypassing agent approved for acquired hemophilia[1]

Count on NovoSeven® RT

For acquired hemophilia, NovoSeven® RT was 95% effective or partially effective as first-line therapy[2]

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): **J7189**[3]

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

FFF Enterprises 800.843.7477 x1903

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.

The most frequently reported adverse reactions in patients treated with NovoSeven® RT are rash, pruritus, urticaria, pyrexia, therapeutic response decreased, and venous thromboembolic events occurring in >.1% to <1% of patients.

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.

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Rx only

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

WARNING: SERIOUS THROMBOTIC ADVERSE EVENTS 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]*

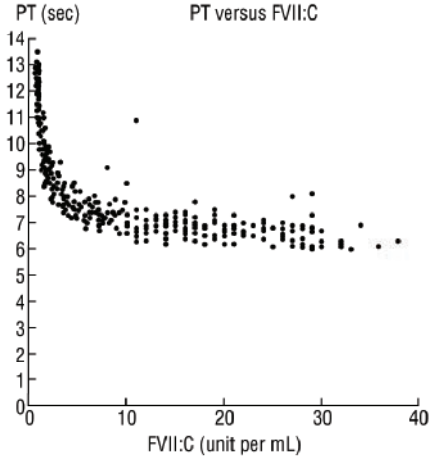
Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

INDICATIONS AND USAGE: NovoSeven® RT, Coagulation Factor VIIa (Recombinant), 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 Factor VII (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 nonactivated 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 units per mL. For FVII:C levels > 5 units per 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 per kg body weight and 90 micrograms per kg body weight following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 units per mL for the two dose levels, respectively.

ADVERSE REACTIONS: The most frequently reported adverse reactions in patients treated with NovoSeven® are rash, pruritus, urticaria, pyrexia and venous thromboembolic events occurring in > 0.1% to < 1% of patients. Therapeutic response decreased has also been reported at a similar rate. It is important that the dosage regimen of NovoSeven® is compliant with the recommended dosage in the package insert. **Clinical Trials Experience:** 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. Thrombotic events following the administration of NovoSeven® occurred in 0.3% of bleeding episodes treated, with the incidence in acquired hemophilia of 4% and in hemophilia patients of 0.2% 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, injection site reaction, headache, hypertension, nausea, vomiting, pain, edema, rash (including allergic dermatitis and rash erythematous), pruritus, urticaria, hypersensitivity, cerebral artery occlusion, 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 reactions that were reported in ≥2% of the 298 patients with hemophilia A or B with inhibitors that were treated with NovoSeven® for 1,939 bleeding episodes.

Body System Reactions	**# of episodes reported** (n=1,939 treatments)	**# of unique patients** (n=298 patients)
Body as a whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Fibrinogen plasma decreased	10	5
Cardiovascular		
Hypertension	9	6

Other reactions reported in 1% of patients were: allergic reaction, coagulation disorder, DIC, edema, fibrinolysis increased, headache, injection site reaction, pain, pruritus, purpura, rash, thrombosis and therapeutic response decreased. Serious adverse reactions occurred in approxi-

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

mately 3% of the patients and included thrombosis, pain, thrombophlebitis deep, pulmonary embolism, therapeutic response decreased, cerebrovascular disorder, angina pectoris, DIC, anaphylactic shock and hepatic function abnormal. The serious adverse reactions of DIC and therapeutic response decreased had a fatal outcome. 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 one study (Study 3), two patients had adverse reactions (acute post-operative hemarthrosis and internal jugular thrombosis). No deaths occurred during the study. In another study (Study 4), four of 24 patients had serious adverse reactions, all being decreased therapeutic response. Two reactions were observed in each treatment arm (bolus injection and continuous infusion). No deaths occurred during the study period. **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. These adverse reactions were reported following the use of NovoSeven® in labeled and unlabeled indications that included individuals with and without coagulopathy: high D-dimer levels and coagulopathy, thrombosis, thrombophlebitis, arterial thrombosis, and thromboembolic events including myocardial ischemia, myocardial infarction, cerebral ischemia, cerebral infarction, renal artery thrombosis, intracardiac thrombus, portal vein thrombosis, thrombophlebitis, peripheral ischemia, deep vein thrombosis and related pulmonary embolism, injection site pain, headache, nausea 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. There have been no confirmed reports on inhibitory antibodies against NovoSeven® or FVII in patients with congenital hemophilia A or B with alloantibodies. 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. 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, 1 non-serious adverse reaction (intracranial hypertension) and 1 serious adverse reaction (IgG antibody against rFVIIa and FVII) were reported. One adverse reaction (localized phlebitis) was reported in the literature. No adverse reactions 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. In compassionate/emergency use programs patients with factor VII deficiency formation of antibodies against NovoSeven® and FVII (frequency: common (≥ 1/100 to < 1/10)) have been reported. In some cases, the antibodies showed inhibitory effect in vitro. Risk factors that may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived factor VII, severe mutation of FVII gene, and overdose of NovoSeven®, were present. Patients with factor VII deficiency treated with NovoSeven® should be monitored for factor VII antibodies. 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, 6 experienced 8 serious adverse reactions. Thrombotic serious adverse events included cerebral artery occlusion, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Additional serious adverse reactions included shock and cerebrovascular accident. Three of the serious adverse reactions had a fatal outcome (shock, cerebral artery occlusion and myocardial infarction).

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 per kg body weight). 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 per kg body weight (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 per kg body weight and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms per kg body weight to 986 micrograms per kg body weight on five consecutive days. There were no reported complications in either case.

More detailed information is available upon request.

For information contact:
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100 College Road West
Princeton, NJ 08540, USA
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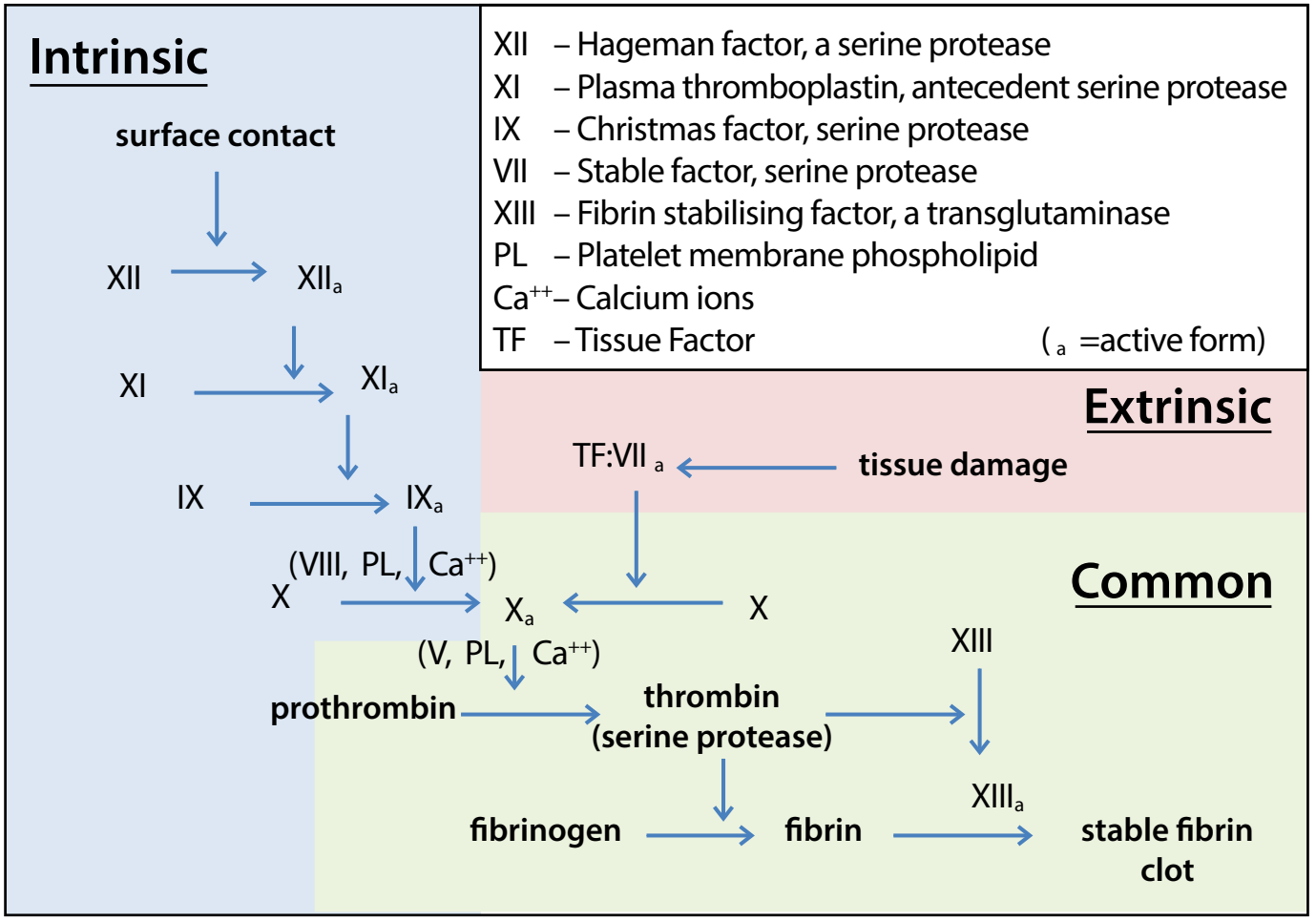
Figure 1. The Three Pathways That Make Up Classical Blood Coagulation



Source: Wikipedia, http://en.wikipedia.org/wiki/File:Classical_blood_coagulation_pathway.png

FVIII and FIX are dependent on FVII, which means if the FVII is replaced in the body, it will activate either FVIII or FIX. A FVII replacement product is also useful in the treatment of hemophilia patients who develop inhibitors or antibody to the replacement factor product. Patients with inhibitors are difficult and expensive to manage. Inhibitors destroy the replacement factor product prior to it working, which necessitates much larger or frequent doses of factor products or puts the patient at risk for bleeding episodes. Another alternative treatment in patients with inhibitors is the use of an anti-inhibitor coagulant complex (AICC). This product contains multiple factors (II, VII, VIII, IX and X) that target several areas in the clotting cascade. These multiple sites of action allow for clot formation without the activation of FVIII or FIX, therefore bypassing the inhibitor.

Little is known about bleeding disorders with the remaining clotting factors. This is due in part to their rarity; there may be one in a million in many cases, and they are often caused by an autosomal recessive trait. Also, it's possible that one of these bleeding disorders may go undiagnosed if patients do not experience a major bleeding episode requiring medical attention during their lifetime. In the event emergency treatment is required, broad-reaching treatments such as fresh frozen plasma, cryoprecipitate or prothrombin complex concentrate (PCC) factor replacement products are typically used. PCCs contain multiple clotting factors along with several proteins, and are used to reverse the anticoagulation effects of warfarin. Currently in the U.S., a three-factor product (II, IX and X) and a four-factor product (II, VII, IX and X) are available; however, they are not used routinely in the treatment of factor disorders due to the high cost, as well as increased risk of thromboembolic events such as pulmonary embolism, deep vein thrombosis, stroke and heart attack. And, even if patients have a positive response to treatment, it becomes difficult to determine the specific factor deficiency that exists, if any, without extensive testing, which may not be widely available.

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Von Willebrand Disease

The most common of all coagulation factor disorders is von Willebrand disease (VWD). CDC estimates that this disorder may affect up to 1 percent of the general population. VWD occurs when individuals have lower-than-normal or non-functioning von Willebrand factor (VWF), which is the protein that helps the platelets become sticky early in the clotting process. Unlike hemophilia, VWD is seen in both men and women, although women are more likely to be diagnosed due to increased bleeding during menstrual cycles or childbirth. Because VWF is carried on clotting FVIII, people with VWD may also have lower levels of FVIII.

Investigators at St. Jude are testing a novel gene therapy approach to treating and, ultimately, curing severe hemophilia B.

Like hemophilia, VWD is further classified into three types — 1, 2 and 3 — based on the amount and/or activity level of VWF that is present. It is imperative to know the specific type of VWD a patient has because the treatment varies for each.

Type 1 VWD is the most common and mildest form of the disease and occurs when individuals have normal functioning VWF but lower levels of it. This is most often treated with desmopressin acetate nasal spray as it causes stored VWF to be released into the blood stream. Type 2 VWD occurs when VWF is present in normal levels but does not function properly. The characteristics of dysfunction will further classify type 2 VWD into four categories: 2A, 2B, 2N and 2M. Type 2 VWD may be treated with desmopressin acetate nasal spray or FVIII product containing VWF. Type 3 VWD occurs when there is little or no VWF present. A patient with this type must be treated with a FVIII product containing VWF and may be treated prophylactically. Patients with VWD may also be prescribed aminocaproic acid, which helps maintain clots once formed.

Ongoing Studies in Coagulation Factor Deficiencies

There are many ongoing studies looking into coagulation factor deficiencies, including their causes and symptoms, as well as the products that treat them. A few examples include:

U.S. Food and Drug Administration (FDA) FVIII Study. FDA's Division of Hematology is responsible for the review of FVIII products used for the treatment of hemophilia A patients. To better characterize these products, it is studying how the structure of FVIII affects the speed with which the liver removes it from the circulation by means of hepatic receptors — proteins on liver cells to which FVIII binds. The results of this study could further improve understanding of the mechanisms of FVIII removal from blood, and facilitate FDA review and approval process for FVIII products, especially of those that are designed to have a long lifetime in the circulation.[1]

St. Jude Children's Medical Center FIX Gene Therapy Study. Investigators at St. Jude are testing a novel gene therapy approach to treating and, ultimately, curing severe hemophilia B. In a Phase I/II trial that differs from previous clinical trials of AAV-mediated gene transfer, the researchers "developed a FIX-expression cassette that is packaged as complementary dimers

Table 1. Hemophilia Severity Classification

	Mild	Moderate	Severe
Amount of Clotting Factor	6-49%	1-5%	< 1%
% of Hemophilia Population	25%	15%	60%
Bleeding Episodes	Injury, trauma, dental	Following injury, procedure or surgery; results in prolonged bleeding	Following injury or trauma
Spontaneous Bleeds	No	Yes	Frequently in joints and muscles
Age of Diagnosis	May be an adult	May depend on family or personal history	By age 1

Table 2. Coagulation Factor Products Available in the U.S.

FVIII Monoclonal	FVIII Recombinant	FIX Monoclonal	FIX Recombinant	FVII	AICC
Alphanate (contains VWF)	Advate	AlphaNine SD	Benefix	NovoSeven RT	FEIBA NF
Hemophil	Helixate	Bebulin VH	Rixubis		
Humate-P (contains VWF)	Kogenate	Mononine			
Koate-DVI	Recombinate	Profilnine			
Monoclate-P					
Xyntha					
Wilate (not indicated for use for FVIII deficiency)					

within a single virus particle.… To avoid antibody-mediated immune responses to AAV, the vectors were pseudotyped with capsid of serotype 8 (AAV8), which is less common in humans than AAV2 is and, thus, less likely to stimulate an immune reaction.… [In addition,] AAV8 preferentially targets hepatocytes (liver cells), so the vector can be injected into a peripheral vein, a simple, noninvasive approach that is safe for patients who are prone to bleeding. Once injected, the vector circulates in the blood until it reaches the liver, where it infects hepatocytes and transfers its genetic information."

Of the first six adult male participants with severe hepatitis B to participate in the trial, five received regular FIX prophylaxis two to three times per week before gene transfer. Participants were enrolled sequentially into one of three dose cohorts (low, intermediate and high). After gene transfer, all six participants showed an increase in FIX levels that was roughly vector dose-dependent. Three of the six participants no longer require FIX concentrate prophylaxis to prevent spontaneous hemorrhage, and three have been able to extend the interval between prophylaxes. These participants had severe hemophilic arthropathy before they entered the study. Because of the results of this study, future efforts will include accruing four more participants, following each participant for a longer period to fully define the benefits and risks of this therapy, and optimizing vector dosing.[2]

CDC Inhibitor Project. CDC is looking into how and why about one-third of those who take blood products to correct coagulation FVIII and FIX deficiencies develop inhibitors, creating far greater difficulty in treating their condition, as well as greatly increasing therapy costs. The goal of the study is to determine whether a change in treatment products (from one type of factor product to another) leads to an inhibitor, whether people with specific gene mutations are more likely to develop an inhibitor, what characteristics make some people more likely to develop an inhibitor than others, why some people develop inhibitors and others do not, and how often inhibitors occur. It is hoped that learning more about why some people develop inhibitors and others do not may help to predict who will develop an inhibitor before treatment is started, which may lead to a decreased rate of inhibitors, decreased healthcare costs, and the licensure of safe and more effective treatment products for people with hemophilia.[3]

Hemophilia: Today and Beyond

It is estimated that the number of new cases of coagulation factor disorders in the world will likely remain constant. However, people with these disorders are living longer today than ever before, and current treatments are both effective and safe. Nevertheless, researchers are looking for better forms of treatment. A great deal of progress has been made over the past 50 years, and now that advances are being made in the fields of biotechnology and gene therapy, it's certainly plausible that there could be a long-term cure for the disease. ❖

AMY EHLERS, *BS, PharmD, BCPS, is the director of pharmacy at NuFACTOR Specialty Pharmacy.*

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BREAKING THE CANCER CODE

Scientific breakthroughs using gene therapy are allowing physicians to take a "precision medicine" approach to treating cancer — with promising results.

By Trudie Mitschang

Finding the cure for cancer has long been an aspiration of medical students, researchers and clinicians alike. Yet, despite many major advances in treatment, none has unlocked the code behind the root causes of cancer — until now. In recent years, there has been an avalanche of findings regarding the genetic mutations that lead to malignant tumors, and these findings are producing the first phase of promising drugs that may control — if not cure — certain cancers.

The first gene mutation was discovered in 2004, a mutation in the EGFR (epidermal growth factor receptor) gene. The ALK (anaplastic lymphoma receptor tyrosine kinase) gene mutation was next, identified using advanced DNA-sequencing technology on lung cancer tumors. Prior to that discovery, a pathologist would identify a patient's lung cancer tumors through a microscope to see if they were of the small-cell or non-small-cell variety. The difference helped determine which regimen of chemotherapy to prescribe.

The discovery of the ALK-gene mutation prompted testing of Xalkori (crizotinib), a brand-named drug manufactured by Pfizer, to see if it worked on the mutation. Pfizer's study of the first lung cancer patients given the drug showed dramatic

improvements, and the U.S. Food and Drug Administration (FDA) approved Xalkori in 2011, four years after the ALK-mutation link was discovered. In an industry accustomed to spending a decade or more waiting for drug approval, the move was a promising one.[1]

In the past few years, discoveries of new gene mutations in cancer research have dramatically accelerated. A 2011 report linked a mutation of a gene called RET to lung cancer, prompting researchers at Memorial Sloan-Kettering Cancer Center in New York to partner with Exelixis Inc., a biotechnology company that was developing a drug called Cometriq (cabozantinib) to treat a rare form of thyroid cancer linked to the RET mutation. That mutation is found in only about 1 percent of lung cancer patients, but Sloan-Kettering moved forward and launched a drug trial. The first few patients tested displayed striking improvements, spurring more research. Discoveries of still more lung cancer mutations have continued at a rapid pace, and the current count is 15, accounting for about 60 percent of all lung cancers, according to some estimates, and researchers expect to find more.[1]

Understanding Gene Therapy

Gene therapy replaces a faulty gene or adds a new gene in an attempt to cure disease or improve the body's ability to fight disease. It holds promise for treating a wide range of diseases, including cancer, cystic fibrosis, heart disease, diabetes, hemophilia and AIDS. Researchers are still studying how and when to use gene therapy, and currently in the United States, gene therapy is available only as part of a clinical trial.[2]

Much of today's cancer research is devoted to identifying missing or defective genes that cause cancer or increase an individual's risk for certain types of cancer. Gene research at the University of Texas MD Anderson Cancer Center, for example, has led to many breakthrough discoveries, including the identification of the mutated multiple advanced cancer gene (MMAC1) that is associated with several common cancers. The center also performed the first successful correction of a defective tumor suppressor gene in human lung cancer.[1] Much of the research to date points to specific potential benefits of gene therapy. These include gene-based treatments that attack existing cancer at the molecular level, eliminating the need for drugs, radiation or surgery, and identifying cancer susceptibility genes in individuals or families that can play a major role in preventing the disease before it occurs.

The focus of most gene therapy research is the replacement of a missing or defective gene with a functional, healthy copy, which is delivered to target cells via a "vector." Viruses are commonly used as vectors because of their ability to penetrate a cell's DNA. These vector viruses are inactivated so they cannot reproduce and cause disease. Gene transfer therapy can also be done outside the body (ex vivo) by extracting bone marrow or blood from the patient and growing the cells in a laboratory. The corrected copy of the gene is introduced and allowed to penetrate the cells' DNA before being injected back into the body. Gene transfers can also be done directly inside the patient's body (in vivo).[3]

In the past few years, discoveries of new gene mutations in cancer research have dramatically accelerated.

Other types of gene therapy include:

- Injecting cancer cells with special genes that make the tumor more receptive to the effects of anticancer drugs
- Introducing the multidrug-resistant gene into bone marrow to make stem cells more immune to the toxic side effects of anticancer drugs.

Gene therapy is a complicated area of research, and there are many variables that can affect outcome. Complications may arise because some cancers are caused by more than one gene, and some vectors, if used incorrectly, can actually cause cancer or other diseases.[3]

Breakthrough Results in Leukemia Study

A study published in *The New England Journal of Medicine* and *Science Translational Medicine* last August spotlighted a clinical trial that took five patients with untreatable cancer and, using their own immune systems, injected genetic material into their white cells, turning them into cancer fighters. The modified white cells then went out in the body and destroyed all the cancer cells. "Cancer cells are similar enough to your normal cells that the T cells cannot recognize it," said Dr. Richard M. Stone, program director of the Adult Leukemia Program at the Dana-Farber Cancer Institute. "By injecting genes into these cells, you're educating the immune system to recognize the cancer."[4]

The treatment success came in a pilot study that was only meant to find out whether the treatment was safe, and to determine the right dose to use in later studies. But, the therapy was significantly more effective than University of Pennsylvania researchers David L. Porter, MD, Carl H. June, MD, and colleagues ever imagined. "Our results were absolutely dramatic. It is tremendously exciting," said Dr. Porter in an interview with WebMD. "These kinds of outcomes don't come around very often. We are really hopeful that we can now translate this into

treatment for much larger numbers of patients and apply this technique to other diseases and many more patients."[4]

The study reviewed only outcomes of patients with acute lymphoblastic leukemia (ALL), but the results could represent a major breakthrough in the fight against all different kinds of cancer. "We have a clinical trial at the University of Pennsylvania with an anti-mesothelin molecule (which marks mesothelioma, ovarian and pancreatic tumors)" explained Dr. Porter. "There are other trials around the country trying to target renal cell carcinoma and myeloma. We are hoping to identify other tumor targets, particularly in other leukemias, to adapt this technology."[4]

A Closer Look at Lung Cancer

Lung cancer is one of the most common and deadliest forms of cancer. Much of the genetic research to date has targeted this particular disease, and the breakthroughs in this area are significant because for decades, lung cancer remained highly resistant to drugs that could extend an average patient's life by even a few weeks. Three decades of research starting in the 1970s uncovered hundreds of potential lung cancer drugs, but produced dismal results; the progress made in diagnosis and treatment increased a lung cancer patient's median survival prognosis by only one month. But, in a recent case study, Kellie Carey, a 45-year-old female patient who was diagnosed with a rare type of lung cancer, underwent experimental treatment that improved her prognosis significantly. Given just three months to live initially, Carey persuaded her physicians to genotype her tumor, and they uncovered that she had an ALK gene mutation that could be targeted by Pfizer's drug Xalkori. By pinpointing her cancer, the drug may have added years to her life, and offered a much better outcome than chemotherapy; within six weeks, two of three cancerous nodules in her lungs had disappeared, and the third had shrunk significantly.[1]

Gene therapy replaces a faulty gene or adds a new gene in an attempt to cure disease or improve the body's ability to fight disease.

Carey's situation was unique. She was "fortunate" enough to be diagnosed with lung cancer in the midst of a revolution in treatment. One thing cancer patients have a limited supply of is time, and when a patient is diagnosed with a cancer mutation that has no approved precision drugs associated with it, the options are to search for a drug in development and then attempt to join its trial. It's a process that could take months or even years, while in some cases there may be off-label (non-FDA-approved) drug options that show promise, but insurers will be unlikely to pay for coverage of such treatments. The good news is that rapid diagnostic advances are making it easier for any doctor to test for the newfound cancers. Tests now can hunt for more than 200 mutations — of lung and other cancers — in one biopsy.

Evidence that precision medicine works will likely broaden its use quickly. A June 2013 report on 1,007 patients with advanced lung cancer whose tumors were sequenced by a group of researchers called the Lung Cancer Mutation Consortium found that 62 percent had alterations suspected of being driver mutations. Currently, there are three drugs on the market for newly discovered lung cancer mutations, while dozens more are in clinical trials. Some approved for other cancers appear effective for specific lung cancers, and drug companies are targeting other mutations of all cancer types.[1]

Promise in the Pipeline

Decoding DNA in tumors is a similar process to how DNA is analyzed to identify criminal suspects. The newly discovered variants in cancer genes have led major cancer centers to revamp their approach to treating cancer and have spurred a rush among drug companies to bring breakthrough medications to market. Companies like Pfizer, Roche Holding AG and Merck & Co. have all thrown their hats in the ring in the race to develop cancer-specific drugs. In 2013 alone, nearly 1,000 cancer drugs were in clinical development, up 52 percent from 2006, according to Pharmaceutical Research and Manufacturers of America. The vast majority of that growth is from drugs targeted at genetic mutations.[1]

"Where we are now is that genetic sequencing of cancers has enabled us to redefine some diseases completely. Lung cancer is the best example. What we find is that lung cancer is a number of different diseases that have very distinct gene mutations," says Hervé Hoppenot, president of the Novartis Oncology Unit. "Once a tumor has been analyzed genetically, we can target each of these mutations very specifically."[5]

Just last year, the FDA established a "breakthrough therapy" designation to hasten approval of experimental drugs that show striking benefits in early trials, including those targeted at cancer mutations. While these new drugs don't yet cure cancer, doctors are encouraged by the possibilities presented by a "precision medicine" approach to treatment that can treat tumors far more effectively than commonplace chemotherapy. A June 2013 study found that lung cancer patients who were

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Important Safety Information

AFLURIA is an inactivated influenza 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.

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.

If Guillain-Barré Syndrome (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.

AFLURIA should be given to a pregnant woman only if clearly needed.

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.

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 brief summary of full prescribing information on adjacent page.

*Afluria is also available in a latex-free, multidose vial formulation containing thimerosal as a preservative.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

INDICATIONS AND USAGE

- AFLURIA is an inactivated influenza 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.

DOSAGE AND ADMINISTRATION

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

Age	Dose/Route	Schedule
5 years through 8 years	0.5 mL IM	One dose or two doses at least 1 month apart*
9 years and older	0.5 mL IM	One dose

*1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

DOSAGE FORMS AND STRENGTHS

AFLURIA is a suspension for injection supplied in two presentations:
- 0.5 mL pre-filled syringe (single dose)
- 5 mL multi-dose vial (ten 0.5 mL doses)

CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine.

WARNINGS AND PRECAUTIONS

- Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years. Febrile events were also observed in children 5 to less than 9 years of age.
- If Guillain-Barré Syndrome (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.
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.
- Immunocompromised persons may have a diminished immune response to AFLURIA.

ADVERSE REACTIONS

- In children 5 through 17 years of age, the most common injection-site adverse reactions were pain (≥60%), redness (≥20%) and swelling (≥10%). The most common systemic adverse reactions were headache, myalgia (≥20%), malaise and fever (≥10%).
- In adults 18 through 64 years of age, the most common injection-site adverse reactions were tenderness (≥60%) and pain (≥40%). The most common systemic adverse reactions were headache, malaise, and muscle aches (≥20%).
- In adults 65 years of age and older, the most common injection-site adverse reactions were tenderness (≥30%) and pain (≥10%).

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

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

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of AFLURIA have not been established in pregnant women or nursing mothers.
- Antibody responses were lower in geriatric subjects than in younger subjects.
- AFLURIA is not approved for use in children less than 5 years of age because of increased rates of fever and febrile seizures. One comparator-controlled trial demonstrated higher rates of fever in recipients of AFLURIA as compared to a trivalent inactivated influenza vaccine control.

Based on July 2013 Version

treated with drugs targeted at their genetically identified varieties lived 1.4 years longer than patients on chemotherapy whose cancers weren't genetically identified. "What we're seeing is the beginning of a revolution in therapeutics," says Janet Woodcock, director of Center for Drug Evaluation and Research. "We can only hope that this gets us to where cancer is managed or curable."[1]

Decoding DNA in tumors is a similar process to how DNA is analyzed to identify criminal suspects.

Research hospitals like MD Anderson, Vanderbilt University and Massachusetts General Hospital are among a growing number of cancer practices that routinely decode the tumor DNA of most patients with advanced cancer. In addition to lung cancer, scientists have decoded tumor DNA from breast, colon, kidney, skin and other cancers, and they are discovering numerous variations they didn't know existed before.

The Role of Genetic Counseling

In May 2013, actress Angelina Jolie announced she had undergone a prophylactic double mastectomy after genetic testing revealed she carried the BRCA1 gene, giving her a roughly 87 percent risk of contracting breast cancer. The news instantly increased awareness of hereditary forms of cancer caused by genetic mutations.

BRCA testing is a genetic test that looks at the sequence, or code, of the BRCA1 and/or BRCA2 genes. Changes or mutations in the genetic code indicate increased cancer risks. The test can be performed on a blood or saliva sample, and genetic counselors and other healthcare providers are tasked with determining whether genetic testing is appropriate for individual patients. Factors that influence the appropriateness of testing include the patient's personal and family history of cancer, age and ethnicity. In general, individuals with a personal or family history of breast cancer appearing before age 50; ovarian cancer at any age; breast cancer in both breasts; male breast cancer; multiple cases of breast cancer within a family; and breast cancer in individuals of Ashkenazi Jewish ancestry should get genetic counseling to determine whether they should be tested.[6]

As was the case with Jolie, a positive test result in BRCA1 or BRCA2 means that the person has a genetic mutation that increases cancer risk. A positive BRCA1 result gives a woman a 60 percent to 80 percent lifetime risk of breast cancer and a 30 percent to 45 percent lifetime risk of ovarian cancer. A positive BRCA2 result gives a woman a 50 percent to 70 percent lifetime risk of breast cancer and a 10 percent to 20 percent lifetime risk of ovarian cancer. In some instances, BRCA2 mutations are also associated with an increased risk of prostate cancer, pancreatic cancer and male breast cancer.[7]

The good news for patients is that BRCA testing is usually covered by insurance if certain criteria are met. Costs can range from $475 to as much as $4,000, and genetic counselors are influential in determining the type of testing required.

Hope on the Horizon

Precision medicine is showing great promise for various types of cancer, although researchers are quick to point out it is not a cancer cure. For one thing, a tumor with a pinpointed mutation doesn't always respond to the drugs used to target it; while the drug often shrinks tumors within weeks, some aggressive tumors can develop resistance and come back with a vengeance, as was the case with Kellie Carey. Carey's lung cancer returned in 2012, and she went off the crizotinib for another regimen of brain radiation, followed by another drug trial for a "next-generation" crizotinib. As of this writing, Carey was also considering a new class of drugs called PD-1 inhibitors that enlist the immune system. Such agents from Merck, Roche and Bristol-Myers Squibb Co. have been creating a buzz among oncologists for use in parallel with the genomic strategy. "The tumor will keep evading our best therapies," said Trever Bivona, a lung cancer researcher at University of California, San Francisco. "Ultimately, we're going to have to get to combination approaches."[1] ❖

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

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Update on Rheumatoid Arthritis

By Jim Trageser

While there is no cure for this autoimmune disease, there are many treatments, including behavioral, medicinal and surgical, and research is ongoing.

Despite a host of recent advances during the last century in treating and preventing many formerly debilitating and/or crippling diseases — in fact, rendering many of them nearly obsolete in the Western world — rheumatoid arthritis (RA) continues to inflict disabling pain and, in many cases, disfigurement on men and women of all ethnicities and socioeconomic classes in the United States and Europe.

Distinct in both cause and physiology from the more common osteoarthritis, RA not only can cause chronic pain, bringing about a diminished quality of life, but also can, if left untreated, slowly destroy the joints in the hands and feet, leading to physical damage that cannot be reversed.[1] As the disease progresses, it may spread to the legs and arms, and then the hips, shoulders and spine. Advanced or severe cases can even cause damage to other tissues of the body, including the eyes, lungs, skin and circulatory system.[2] The condition is also linked to early mortality.[3]

The causes of RA remain unclear, with most research now indicating a possible genetic predisposition that can be triggered by an unknown number of combinations of catalysts.[4] And, while there is neither prevention nor cure currently available, there are many treatments that can ease the pain and slow or even halt the destruction of joint structures.

What Is RA?

RA is an autoimmune disease in which the body's defenses attack the lining that surrounds the joints of the hands and feet.[2] Specifically, the body's immune system attacks the synovial membranes, the tissue that surrounds joints with capsules — in the fingers and toes, for instance. As the membrane is attacked by the immune system, it swells, causing pain and loss of flexibility. Over time, the pressure from the swollen synovium causes the cartilage and bone in the joints to begin to break down, causing disfigurement and further loss of function.[5]

Advanced cases can cause other health problems as the body struggles to deal with the autoimmune attacks on itself. The lungs may develop fibrosis, the kidneys may begin to develop amyloid deposits, the eye sockets can dry out making them more susceptible to infection and other vision problems, and the swollen joints may cause a rise in blood pressure that can raise the patient's risk of heart attack or stroke.[6]

RA can occur at any stage of life, but most commonly it is seen in patients age 40 and older. The Mayo Clinic estimates that between 3 percent and 4 percent of people will develop RA at any point in their life. Women are statistically two to three times as likely as men to develop RA. In addition, women who have given birth and breast-fed are at slightly lower risk of developing RA, although researchers do not understand why this is true.[3] Smokers are also at heightened risk of contracting RA — again, for reasons not yet understood.

Symptoms of RA

The earliest symptoms of RA are often similar to or the same as those for the more common age- and injury-related osteoarthritis: stiffness and pain in the joints, particularly upon waking in the morning.[7] However, depending on the specific progression and the stage at which symptoms are first noticed, RA also may cause small, noticeable bumps (known as rheumatoid nodules) under the skin of the arms. Fingers or toes also may be swollen and warm to the touch, and patients may notice fatigue or have a fever.

It is recommended that anyone suffering chronic joint paint see a doctor to get an early and accurate diagnosis.

Diagnosing RA

Physicians seeing a patient will often face several challenges in accurately diagnosing RA if the disease is still in its early stages. There is currently no single test that will positively identify a case of RA. As previously mentioned, the early symptoms are similar to osteoarthritis and other joint diseases: pain and swelling in the joints. X-rays or other scans taken during the early stages of the disease will not yet reveal joint damage, as that takes time to develop.

RA can occur at any stage of life, but most commonly it is seen in patients age 40 and older.

Doctors may order one or more of several blood tests to determine if certain factors associated with RA are present. A test for the rheumatoid factor (RF) will detect if a patient's bloodstream contains an antibody consistent with RA. However, many patients with RA never show RFs, and others with RF present never develop RA.[5] Anti-cyclic citrullinated peptides also can be looked for, as they often show up in patients with RA. Another test, for erythrocyte sedimentation rate, can help confirm the presence of inflammation in the patient's body.[8] While none of these tests is as clear-cut as, say, a biopsy confirming a tumor is benign or a culture indicating an infection, a combination of them will give a physician a fairly good indication of whether a patient has RA.

Treating RA

Currently, there is no cure for RA. Doctors do, however, have numerous options available to help ease a patient's discomfort

and to slow the progression of the disease. For most patients, this will be a combination of behavior (diet and exercise), medication (immune suppression, swelling reduction, pain control) and equipment (braces).

Patients with RA can almost universally benefit from a carefully monitored regimen of exercise and rest. Regular exercise will strengthen the musculature around the joints, providing additional stability and support. However, when RA is flaring and there is significant inflammation, rest is indicated.[9] The use of a brace or splint can help provide additional support to joints affected by RA. In addition, the use of self-help devices such as zipper pullers or long-handle shoe horns can relieve pain and wear on joints.[7]

There is currently no single test that will positively identify a case of RA.

While exercise and reducing stress on joints are important components of treating RA, modern medications also are an important part of most treatment programs. Among the types of medications used in treating RA are:

• Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to reduce swelling and alleviate pain. Over-the-counter varieties include ibuprofen (Advil, Motrin) and naproxen sodium (Aleve). Prolonged usage can increase the risk of liver damage or kidney damage, cardio issues or stomach irritation.[9]

• Corticosteroids may be used for short durations to provide quick relief, but carry the risk of more severe side effects such as diabetes, loss of bone density and cataracts.[9]

• Disease-modifying antirheumatic drugs (DMARDs) help prevent serious joint deterioration and permanent disfigurement, but need an even higher level of monitoring due to the risks associated with them — from liver failure to lung infections.[9] Among the DMARDs used in treating RA are hydroxychloroquine, leflunomide, methotrexate and sulfasalazine. While they work in different ways, each slows the disease by interfering with the way the body's immune system is attacking the joints.[5]

• Immunosuppressants are used to weaken the immune system as a whole. The risk of acquiring other infections when using drugs such as azathioprine and cyclosporine means they are generally reserved for severe cases of RA when other treatments are not providing effective relief.[9]

• TNF-alpha inhibitors slow the production of certain substances that cause inflammation. Again, these increase the risk of other infections in the patient.[9]

When behavior modification and medications are not enough to stop the progression of the disease, a physician may recommend surgery to restore function and/or ease pain. Joint replacement surgery, tendon reconstruction and joint fusion are all strategies employed as a last resort to help patients with RA.[9]

Research

Current research into RA is focused in four main areas: locating the genes that may predispose some people to developing RA; uncovering the specific triggers that cause RA to develop; understanding the specific molecular processes that occur in the joints of patients with RA; and finding more effective treatments.

Until we understand exactly how RA develops, prevention is not possible. However, as our understanding of the processes of RA grows, so do the possibilities for treatment. In 2012, the drug tofacitinib was approved for treatment of RA. It works by blocking a specific activity of the immune system that leads to joint destruction. Similar research is looking into other facets of the immune system to develop drugs that will slow or stop RA without compromising a patient's overall immune protection.

Any prevention or cure is likely decades away given the complexity of RA. However, treatments continue to improve all the time, providing physicians a growing array of resources to assist them in helping their patients. ❖

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Thirty Years On, IVIG Clinical Research Keeps Rolling

BY KEITH BERMAN, MPH, MBA

JUST MONTHS AFTER the first commercial intravenous immune globulin (IVIG) product was introduced in 1981, an expert workshop was convened to review its "use and potential." In addition to reports on the use of IVIG in heart and bone marrow transplant patients, presenters addressed its protective benefits and dosing issues for patients with primary immunodeficiency disorders.[1] And that was it.

So it is difficult to imagine that, more than 30 years later, those workshop participants could have foreseen that IVIG remains the subject of intensive clinical research interest, with published case reports, case series and controlled clinical trials now numbering in the thousands. Or that in 2014, IVIG products are being evaluated in dozens of U.S. and international clinical trials for hard-to-treat disorders as diverse as scleroderma and sickle cell crisis.

It has long been appreciated that IVIG preparations, purified from large pools of donor human plasma, contain a broad range of "immune" IgG antibodies directed against bacteria and other pathogens. IVIG, as well as subcutaneously administered immune globulin (SCIG), continues to provide effective long-term passive immunity to protect children and adults with primary and selected secondary humoral immunodeficiency disorders.

But the secret to the breadth and longevity of research interest in IVIG largely lies elsewhere: the product's vast repertoire of "natural" IgG antibodies

that collectively comprise as much as 95 percent of total IgG in our circulation and extracellular compartment. These natural antibodies have a multiplicity of key immunoregulatory functions, including but not limited to:

- Interference with autoantibody production
- Neutralization of self-directed autoantibodies
- Downregulation of macrophage and other phagocyte activity

• Attenuation of inflammation through known mechanisms that include modulation of cytokine production and binding to activated complement components

• Interference of the interaction between T cells and antigen-presenting cells

Added to this are IgG antibodies that appear to be ubiquitous in human blood serum, but whose functions are not well understood. As with innately produced "natural" IgM autoantibodies whose function appears to involve clearing tissues of post-apoptotic cellular debris, we are born with many thousands of natural IgG autoantibodies that are multiply reactive with self-antigens on cells that mediate immunity, as well as other antibodies. IgG autoantibodies were thought to be solely involved with the etiology of autoimmune diseases. But it is now evident that IgG, as well as IgM, autoantibodies are purposefully produced by the healthy immune system to help regulate itself.

IgG autoantibody counts have been shown to rise with advancing age. However, in a recent study examining persons with three major autoimmune neurological disorders — Alzheimer's disease (AD), multiple sclerosis (MS) and Parkinson's disease (PD) — a U.S. investigative team found that IgG autoantibody diversity was significantly diminished — not increased — in each of those populations as compared with healthy control subjects (Table 1).[2] Adding to the puzzlement is the fact that these observed drops in IgG autoantibody count in AD, MS and PD directly conflict with a pattern of increasing IgG autoantibody count with age in the general population.

The decades-long interest in the clinical applicability of IVIG has undoubtedly been fueled by growing awareness of the diverse roles of IgG in immunoregulation.

These and innumerable other unanswered questions underscore how little we know about the role of natural human IgG antibodies both in the regulation of normal immunity and in the suppression of autoimmunity.

What's Hot in IVIG Clinical Research

The decades-long interest in the clinical applicability of IVIG has undoubtedly been fueled by growing awareness of the diverse roles of IgG in immunoregulation, and further abetted by reliance on use of toxic immunosuppressive drugs that reflects our limited understanding of the underlying pathophysiology of most human autoimmune disorders. But perhaps the biggest reason behind the excitement over IVIG is the results themselves: an ever-expanding body of evidence that already has affirmed or strongly suggested health outcome benefits of IVIG administration in a remarkably diverse range of difficult-to-treat autoimmune and inflammatory disorders.

To date, controlled trials have established beneficial health outcomes of IVIG for at least a dozen autoimmune and inflammatory disorders. Based on extensive reported case experience, IVIG is also widely prescribed in numerous other autoimmune neuropathies, neuro-

Table 1. Influence of Health Status on IgG Autoantibody Counts[2]

	N	Mean age	Mean sample IgG autoantibody count	P (versus control)
Alzheimer's disease	36	79.4	1,515	7.64 E-06
Parkinson's disease	48	68.0	1,833	3.50 E-03
Control subjects	47	61.1	2,435	
Multiple sclerosis	7	48.4	2,093	0.044
Control subjects	10	52.5	3,119	

Table 2. Autoimmune and Inflammatory Diseases for Which IVIG Is Commonly Prescribed

Autoimmune neuromuscular diseases
- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Lambert-Eaton myasthenic syndrome
- Multiple sclerosis with relapsing-remitting disease
- Multifocal motor neuropathy
- Myasthenic crisis
- Exacerbations of chronic severe myasthenia gravis
- Stiff-person syndrome

Inflammatory myopathies
- Dermatomyositis
- Kawasaki disease
- Polymyositis

Hematological disorders
- Autoimmune hemolytic anemial
- Fetal alloimmune thrombocytopenia
- GVHD prevention in stem cell transplant
- Immune neutropenia
- Immune thrombocytopenic purpura
- Polymyositis

Autoimmune mucocutaneous blistering diseases
- Bullous pemphigoid
- Pemphigus vulgaris and pemphigus foliaceus
- Mucous membrane pemphigoid
- Epidermolysis bullosa acquisita

muscular junction disorders, hematological disorders, inflammatory myopathies, mucocutaneous blistering diseases and solid-organ transplant-related disorders (Table 2).

Among many clinical trials currently in progress are several that stand out for their potential to expand the therapeutic utility of IVIG:

Vaso-occlusive crisis in sickle cell disease (SCD). Vaso-occlusive crisis is the most common complication of SCD, and can progress to life-threatening acute chest syndrome. The most affected 5 percent of SCD patients experience from three to 10 crisis episodes per year.[3] Other than opioid analgesics to blunt pain resulting from microvascular occlusion, there is currently no specific treatment for this condition.

In a mouse model of SCD, commercial IVIG preparations have been shown to rapidly reduce adherent leukocyte numbers and dramatically inhibit interactions between red blood cells and white blood cells, resulting in improved microcirculatory blood flow and survival rates.[4]

Encouraged by these animal study findings, researchers at Montefiore Medical Center in New York City initiated a Phase I/II randomized, masked, double-blind clinical trial several years ago, with an enrollment goal of 60 patients between ages 12 years and 65 years who require hospital admission for a pain episode. Patients will receive either a single dose of up to 800 mg/kg of IVIG or normal saline. Primary and secondary endpoints include duration of the pain crisis and total opioid use, respectively. The study is on schedule to complete data collection for the primary outcome assessment in July 2014.

Idiopathic cardiomyopathy. Persistence of parvovirus B19 has been associated with progressive cardiac dysfunction leading to idiopathic cardiomyopathy (ICM). A 2010 pilot study evaluating high-dose IVIG (2 g/kg) therapy in 17 consecutive patients with ICM, symptomatic heart failure and biopsy-proven endocardial parvovirus B19 (PVB19) documented a significant improvement in ejection fraction from a pretreatment baseline of 34 ± 3 percent to 41 ± 3 percent six months after IVIG administration.[5]

This same team of Dutch investigators is currently about midway through a randomized, double-blind placebo-controlled trial designed to evaluate the same dose of IVIG (divided over four days) in 50 patients with chronic symptomatic ICM and a high biopsy-confirmed PVB19 load. The estimated primary completion date is November 2015.

Systemic sclerosis (systemic scleroderma). In addition to skin thickening resulting from vascular injury and subsequent fibrosis, patients with the diffuse form of systemic scleroderma are at risk of developing widespread, severe internal organ involvement. Spontaneous

improvement is very uncommon, and current immunosuppressive drug options targeting kidney, lung, skin and other organ diseases are of very limited value.

Thirty years after its quiet introduction, unabated global research interest in IVIG reflects just how much remains unknown about its therapeutic potential.

Encouraged in part by a 100 percent complete or partial response rate to high-dose IVIG in patients with scleromyxedema, a very rare scleroderma-like fibrosing disorder,[6] investigators at Johns Hopkins and Georgetown University hospitals initiated a three-to-one randomized, albumin placebo-controlled, double-blind trial in April 2013 to evaluate a six-month course of monthly high-dose (2 g/kg) IVIG in 24 patients with diffuse systemic sclerosis. Effects on skin will be the primary outcome measure; other measured outcomes will include pulmonary function, as well as muscle, joint, inflammatory and various laboratory testing parameters. Findings from a very recent study by Japanese researchers offer evidence that multiple courses of IVIG may be needed to achieve efficacy in many patients with the diffuse form of the disease.[7]

Bullous pemphigoid (BP). A large majority of adult BP patients (33 of 41) in a recent literature review experienced rapid partial or complete response to IVIG therapy after failure or intolerance to standard immunosuppressive drug therapy. It also appears that a shorter disease duration prior to IVIG therapy strongly correlated with a shorter time to complete response.[8]

A Japanese Phase III study completed in September 2013 took the next logical step by randomizing 56 patients with BP unresponsive to corticosteroids to receive high-dose IVIG (400 mg/kg/day for five days) or placebo. Potential benefits could include more rapid induction of remission, more durable remission and reduction in corticosteroid-related adverse events. Available evidence together with findings from this first randomized controlled trial of IVIG in BP may prompt a re-evaluation of whether, as has recently been proposed for pemphigus,[9] addition of IVIG should be considered earlier in the management of BP and other mucocutaneous blistering diseases.

Yesterday, Today and Tomorrow: A Cornucopia of IVIG Research

The functionality and excellent safety and tolerability of IVIG will continue to attract interest among clinicians concerned with poor efficacy, relapse and adverse events associated with corticosteroids and cytotoxic drugs still relied on as first-line therapy against most autoimmune disorders. Where past studies have failed to confirm case reports of significant benefit for some conditions, could there be overlooked disease subcategories that respond well to IVIG, warranting a new trial or an evaluative course of therapy strategy? Might more aggressive or extended dosing in certain conditions potentially deliver the quantity of deficient immunomodulatory IgG antibodies needed to overcome autoimmune and inflammatory dysregulation?

Thirty years after its quiet introduction, unabated global research interest in IVIG reflects just how much remains unknown about its therapeutic potential. But that should be little wonder when one stops to consider that IVIG — quite literally three-quarters of our humoral immune system supplied in small glass vials — is like no other therapeutic ever introduced into the medical armamentarium. ❖

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Leading the Way with Lifesaving Innovation

"They tried to kill me, and instead, they put me on the map — all of a sudden, everyone knew about this woman who stood up to the pharmaceutical industry."

— Dr. Manon Cox, president and CEO, Protein Sciences Corp.

BY TRUDIE MITSCHANG

IN AN INDUSTRY dominated by formidable corporations and well-established manufacturing protocols, a small Connecticut-based company has begun quietly claiming the spotlight. In early 2013, Protein Sciences Corp. made headlines when its much-anticipated Flublok influenza vaccine became the first U.S. Food and Drug Administration (FDA)-approved recombinant influenza vaccine. Bringing the product to market has been a labor of love decades in the making, and strategically positioned on the frontline of this effort is the company's visionary and tenacious leader, Dr. Manon Cox.

Dr. Cox joined Protein Sciences in 1998 as director of business development, became chief operating officer in 2000 and CEO in 2010. Her passion for innovation and desire to make a difference within an industry bogged down by dated technology has been a driving force behind the company's remarkable success. "We basically asked ourselves why today's vaccines should be made using technology from the 1940s," says Cox. "We saw an opportunity to make a real difference in the influenza field and solve the problems associated with the traditional egg-based technology used to make flu vaccines. And, we did."

Pioneering DNA Technology

As a company, Protein Sciences has been transforming the biopharmaceutical landscape through the application of its patented Baculovirus Expression Vector System (BEVS) technology. BEVS is currently being used to develop new, innovative products that can save lives and improve health around the world.

Thirty years ago, scientists at Protein Sciences developed and patented BEVS, which has the ability to harness the power of cell culture, programming cells to produce large quantities of specified proteins. Since the active ingredients in vaccines are proteins, the company can use BEVS to make just the active ingredients of vaccines, without growing pathogens.

The advantage of developing BEVS-generated influenza vaccines is that vaccines can be produced in a mere two months; are not limited by strain origin; do not require biocontainment; and are 100 percent egg-free. In addition, the active ingredient in the BEVS influenza vaccine matches the circulating influenza virus since it is made using DNA technology rather than propagating the influenza virus in eggs.

"Our vision was to create a vaccine using a streamlined manufacturing process where highly pure vaccines could be made by design, using modern DNA technology and cell culture in a sterile, well-controlled environment," says Cox. "Flublok is our first-of-its-kind influenza vaccine containing no egg protein, influenza virus, preservatives, antibiotics, gelatin or latex — it's an accomplishment we are extremely proud of."

Sassy Mouth Photography

As chief operating officer of Protein Sciences, Dr. Mannon Cox has devoted her energy to creating a first-of-its-kind influenza vaccine. Now, she is setting her sights on developing vaccines for other diseases with the company's innovative technology platform.

The Path to Approval

Anyone who has ever brought a vaccine to market knows it is no small feat. But, for a company with fewer than 50 employees at the time, navigating the approval process was very much a David versus Goliath undertaking, wrought with setbacks, detours and even hostile takeover attempts. "We are a young innovative company, and we are going up against the status quo," says Cox. "At one point, the National Institutes of Health asked us to do an additional study for our proposed vaccine, at a cost of over $20 million. We hired a banker to help raise funds, and during the process, our entire company was almost sold out from under us."

Cox explains that when shareholders rejected the offer to buy the company, they faced a series of lawsuits, including some filed against her personally: "It was a very difficult time, but some say what does not kill you makes you stronger. They tried to kill me, and instead, they put me on the map — all of a sudden, everyone knew about this woman who stood up to the pharmaceutical industry."

Making a Difference One Vaccine at a Time

As a biology student, Cox recalls taking a trip to Africa and witnessing the devastation of entire villages following the first wave of the HIV epidemic. Through her studies, Cox had become fascinated by the efficacy of vaccines and their power to eradicate disease, and wondered idealistically if she could one day make a significant contribution within this lifesaving industry. "I began learning about the ins and outs of vaccine development and what dealing with the FDA entails, so I wisely decided to start with something less challenging than a vaccine for HIV," she says. "I devoted my energy to a new influenza vaccine, but ultimately my desire is to create vaccines for diseases that, like HIV, are killing people in developing countries."

Cox says her immediate goal is to expand the delivery systems for Flublok and introduce new vaccines into the company portfolio using the BEVS technology platform. Innovations in the pipeline include a vaccine for rabies and an infused therapy for spinal cord injuries. "This technology has tremendous potential in so many different arenas, and is already being used for the development of a wide range of vaccines and therapeutics," adds Cox. In addition to Flublok, two other BEVS-generated products have progressed through Phase II clinical development, including a therapeutic vaccine for type I diabetes and a gene therapy for lipoprotein lipase deficiency

Passionate about her company's mission, Cox says as a leader she strives to inspire and motivate her team to collectively accomplish things they might never achieve individually. She encourages team work and advises young employees to go the distance in their careers in favor of bouncing from job to job. While maintaining a "can do" attitude in the face of opposition can be challenging at times, Cox says it's easier when the company's primary product has lifesaving potential: "In a way, it's easy to stay motivated when you do something as important as what we do in our company. It's one thing to treat people who are sick, but vaccines are the only way to eradicate disease. We don't have polio anymore because of vaccines. We're developing vaccines that save lives. It's an exciting time to be a part of such a vibrant, growing industry." ❖

"Flublok is our first-of-its-kind influenza vaccine containing no egg protein, influenza virus, preservatives, antibiotics, gelatin or latex — it's an accomplishment we are extremely proud of."

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

Fibromyalgia: A Patient's Perspective

BY TRUDIE MITSCHANG

IT ALL STARTED with a positive tuberculosis test. In 2002, Linda Thornrose was working in a physician's office when a routine exam catapulted her into a two-year ordeal of complex treatments and eventual liver failure. Two years later, Linda was diagnosed with combined variable immune deficiency, a primary immune deficiency disease. Her treatment plan centered on intravenous infusions of immune globulin every 28 days, but rather than getting better, Linda's symptoms grew worse. "I was becoming more and more fatigued and began having pain all over my body. Since there was a history of osteoarthritis in my family, I made an appointment with a rheumatologist," recalls Linda. "Thank God for my physician, who gave me a thorough exam. He said that I tested positive for all 'trigger points' of fibromyalgia; I had never even heard of it."

Linda's physician prescribed Vioxx, a popular arthritis treatment medication, which seemed to ease her pain. However, that drug was soon taken off the market, and she was switched to a second and, finally, a third prescription that led to a severe outbreak of hives. Linda was also prescribed various antidepressants that resulted in weight gain and, later, withdrawal symptoms. Eventually, she was prescribed Savella (milnacipran HCl tablets) and is currently on 25 mg BID, along with daily narcotic pain medications.

Because of her worsening health, Linda left her job in 2006. She says the cycle of prescription medications and troubling side effects continued as her physicians experimented to try to find combinations that would produce the best results. "The pain never goes totally away, and I really hate all the humiliation that comes with having to take so many narcotics," she explains.

A Misunderstood Illness

Like many fibromyalgia patients, Linda has encountered the perception that the disease is all in her head. Even friends and family have turned away, frustrated by her inability to make and keep plans. Linda also deals with chronic insomnia, a common condition associated with fibromyalgia, and the resulting exhaustion and fatigue make it difficult to function. "Shortly after my diagnosis, I went in for a sleep test since sleep problems are a common issue that can make symptoms worse," says Linda. "My results showed I stopped breathing an average of 33 times per hour. I was put on a CPAP mask for sleep, and it has been a big help — once I get to sleep."

Diagnosed in 2004 with fibromyalgia, Linda Thornrose is always in pain and deals with chronic insomnia. What she wishes most is that people would understand that this is a real disease and offer some kindness.

Linda feels fortunate that her doctor suspected fibromyalgia early on, and advises patients who display common symptoms of the illness to seek an evaluation from a rheumatologist. She also encourages online research and suggests patients seek out doctors who specifically treat fibromyalgia. "I was blessed to have a good doctor who diagnosed me right away, but I have learned so much more from my own research," she says.

When it comes to being misunderstood, Linda says she wishes friends and physicians would recognize that this is a real disease and that it is chronic. "Everyone means well, they just don't understand that there is nothing I can do to make myself better," she says. "Just a word of kindness, a hug, offering to run an errand or bring a meal over during my difficult days would be great. Those types of things mean much more than always trying to fix me with advice or assuming I can do something to make it go away." ❖

What is Fibromyalgia?

Fibromyalgia is the most common musculoskeletal condition after osteoarthritis. Its characteristics include widespread muscle and joint pain and fatigue. Fibromyalgia can lead to depression and social isolation. More than 12 million Americans have fibromyalgia, most of them women. Symptoms include:

- Anxiety or depression
- Decreased pain threshold or tender points
- Incapacitating fatigue
- Widespread pain
- Abdominal pain
- Chronic headaches
- Dryness in mouth, nose and eyes
- Hypersensitivity to cold and/or heat
- Inability to concentrate (called "fibro fog")
- Numbness or tingling in the fingers and feet
- Stiffness

Fibromyalgia: A Physician's Perspective

JACOB TEITELBAUM, MD, is director of the Fatigue and Fibromyalgia Practitioners Network and author of the popular free iPhone and Android application Cures A-Z and best-selling books *From Fatigued to Fantastic!*, *Pain Free 1-2-3 — A Proven Program for Eliminating Chronic Pain Now*, the *Beat Sugar Addiction NOW!* series, *Real Cause, Real Cure*, and *The Fatigue and Fibromyalgia Solution*. He is the lead author of four studies on effective treatment for fibromyalgia and chronic fatigue syndrome, and he does frequent media appearances including "Good Morning America," CNN, Fox News Channel, the "Dr. Oz Show" and "Oprah & Friends." His website is www.endfatigue.com.

BSTQ: You are a former fibromyalgia patient. What was that like?

Dr. Teitelbaum: I came down with chronic fatigue syndrome and fibromyalgia during medical school. Being on the other side of the white coat was quite the eye-opener. After an extensive series of tests could not pinpoint the cause of my post-viral fatigue, my medical school professors simply presumed that I must be having "depressed med student syndrome."

BSTQ: Why are fibromyalgia patients so frequently misdiagnosed?

Dr. Teitelbaum: Because there is no lab test that is specific for diagnosing fibromyalgia, and, like most immune dysfunctions, it is an illness that predominantly affects women. We saw the same thing years ago with multiple sclerosis, which used to be called "hysterical paralysis." Rheumatoid arthritis and lupus were also considered illnesses of neurotic women. Once a specific test was developed for each of these illnesses, these patients magically went from being neurotic to having a real disease. It's sad, but the perspective can be understood by looking at the medical word *hysteria*, which comes from the Latin *hystero*, or uterus. Even with half of physicians now being women, this old and abusive medical stereotype persists.

BSTQ: How does your approach to treatment differ from traditional medicine?

Dr. Teitelbaum: Traditional medicine offers three medications that essentially are Band-Aids for pain, and then tells people to live with the illness, while insinuating that they are crazy and simply need to exercise more. Our research and clinical experience, and that of many other physicians, has shown that fibromyalgia represents an energy crisis where people have essentially "blown a fuse" called the hypothalamus. The hypothalamic circuit breaker controls sleep, which is why the symptom of severe insomnia in the presence of widespread pain and fatigue is so helpful in diagnosing the illness. Our approach helps to restore energy production while eliminating unnecessary energy drains, allowing the hypothalamic circuit breaker to turn back on. Fortunately, a wide array of natural therapies can be very helpful for people with fibromyalgia.

Fibromyalgia represents an energy crisis where people have essentially "blown a fuse" called the hypothalamus.

BSTQ: What changes are needed by our medical system to effectively treat chronic illness?

Dr. Teitelbaum: Both my personal experience and that of countless people with fibromyalgia have shown that other healthcare disciplines, from acupuncture to naturopathy and nutrition, have much to offer in terms of helping people with fibromyalgia. Yet, most physicians have not a clue regarding the rationale behind other health modalities. This can change if health practitioners from different backgrounds simply start to speak with each other and share their experiences and perspectives. ❖

Dr. Jacob Teitelbaum, a specialist in chronic fatigue syndrome and fibromyalgia, uses a holistic approach to treating fibromyalgia called S.H.I.N.E.

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

BioResearch

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

IVIG in Combination with Corticosteroids Reduces Morbidity and Mortality in Toxic Epidermal Necrolysis

Low-dose intravenous immune globulin (IVIG) added to a course of corticosteroids has been found to be superior to corticosteroid therapy alone in resolving toxic epidermal necrolysis (TEN) and reducing associated mortality risk, according to a clinical study by Indian investigators. Thirty-six consecutive TEN patients were alternately assigned to 1) low-dose IVIG (from 0.2 to 0.5 g/kg) and a rapidly tapering course of intravenous dexamethasone (from 0.1 to 0.3 mg/kg/day) tapered in one to two weeks or 2) the same dose range of dexamethasone only.

The two groups of 18 patients had comparable baseline characteristics, including age, sex ratio, score of toxic epidermal necrosis (SCORTEN), body surface area involvement and treatment interval. The time to arrest of disease progression and for re-epithelialization was significantly shorter in the IVIG/dexamethasone group (P = 0.0001 and P = 0.0009, respectively). While the duration of hospital stay and death rate was also lower in the IVIG/dexamethasone group, the difference was not statistically significant. However, SCORTEN-based standardized mortality ratio (SMR) analysis revealed that combination therapy reduced the probability of dying by 82% (SMR = 0.18 ± 0.36). The difference in SMR was statistically significant (P = 0.00001).

No significant side effects were associated with either treatment modality. The investigators concluded that "combination therapy with low-dose IVIG and steroids is more effective in terms of reduced mortality and faster disease resolution when compared to steroids alone in TEN."

Jagadeesan S, Sobhanakumari K, Sadanandan SM, et al. Low dose intravenous immunoglobulins and steroids in toxic epidermal necrolysis: a prospective comparative open-labelled study of 36 cases. Indian J Dermatol Venereol Leprol *2013 Jul-Aug;79(4):506-11.*

Influenza Vaccination Associated with Reduced Risk of Major Adverse Cardiovascular Events: Meta-Analysis

With the goal of determining if seasonal influenza vaccination is associated with prevention of cardiovascular events, Canadian investigators conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) available on MEDLINE (1947 – August 2013), EMBASE (1947 – August 2013) and the Cochrane Library Central Register of Controlled Trials (inception – August 2013) that examined major cardiovascular event experience in high-risk patients given influenza vaccine, placebo or no treatment. Analyses were stratified by subgroups of patients with and without a history of acute coronary syndrome (ACS) within one year of randomization.

Five published and one unpublished RCTs of a total of 6,735 patients (mean age 67 years; 51.3 percent female; 36.2 percent with a cardiac history; mean follow-up time 7.9 months) were included in the meta-analysis. Influenza vaccine administration was associated with a lower risk of composite cardiovascular events (2.9 percent vs. 4.7 percent; RR 0.64; 95 percent CI, 0.48 – 0.86; P = 0.003) in the five published trials. A treatment interaction was detected between patients with (RR 0.45 [95 percent CI, 0.32 – 0.63]) and without (RR 0.94 [95 percent CI, 0.55 – 1.61]) recent ACS. Results remained similar with the addition of unpublished data.

The study authors concluded that the use of influenza vaccine was associated with a lower risk of major adverse cardiovascular events. The greatest treatment effect was seen among the highest-risk patients with more active coronary disease.

Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA *2013 Oct 23;310(16):1711-20.*

Dermatomyositis with Isolated Severe Skin Lesions Responds to IVIG Therapy

Intravenous immune globulin (IVIG) is a recommended therapy for corticoresistant or corticodependent dermatomyositis (DM), but only a few cases of difficult-to-treat DM with isolated skin involvement have been reported. Investigators at Hôpital Saint Louis in Paris conducted a retrospective single-center study of 27 patients treated with IVIG for severe DM skin lesions and no or minor muscle involvement, following failure of photoprotection and at least one line of treatment.

Nineteen of the 27 DM patients exhibited a major response to treatment with IVIG. Four patients experienced a partial response, and the remaining four patients had no response. The mean number of IVIG courses was 4.8 (range 1 to 15). Ten of the 19 responders (53%) relapsed, with a median time of 6.2 months after the last IVIG course; six of these patients were successfully re-treated with a new course of IVIG therapy.

The investigators concluded that IVIG may be an effective and safe treatment for DM with isolated skin involvement. Relapse occurred frequently in this patient series, but treatment with a new course of IVIG was successful. They called for controlled studies to confirm these results.

Bounfour T, Bouaziz JD, Bézier M, et al. Clinical efficacy of intravenous immunoglobulins for the treatment of dermatomyositis skin lesions without muscle disease. J Eur Acad Dermatol Venereol *2013 Aug 1 [Epub ahead of print].*

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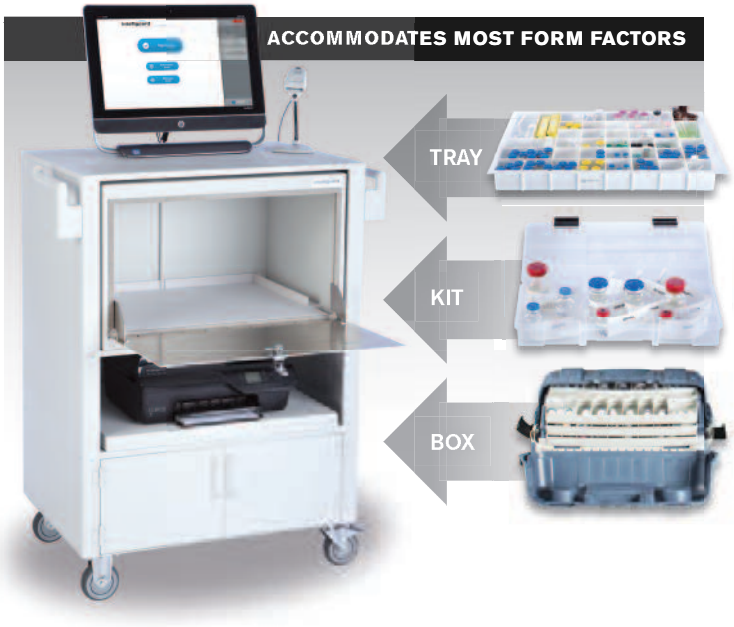

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BioProducts

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New Program Monitors Consigned Medications with RFID

FFF Enterprises launched its Verified Inventory Program-Consignment (VIPc), which tracks the condition and use of consigned medications through the use of radio frequency identification (RFID). VIPc provides cabinets equipped with advanced RFID technology to monitor inventory, eliminate carrying costs and invoice providers only when products are used. The system continuously monitors critical-care inventory to ensure the right amount of product is kept on hand and automatically replenished as it is used. Furthermore, VIPc preemptively pulls and replaces product well before its beyond-use date, so there is no liability for expired product. "Our previous policy was influenced by our strongly held belief that unused, consigned products that are returned from a consignee are subject to pedigree requirements, even though title of ownership did not transfer," explained Patrick M. Schmidt, chief executive officer, FFF Enterprises, Inc. "VIPc takes our Guaranteed Channel Integrity to the next level by enabling us to track, trace and verify a product's moment of use and previous storage location and conditions — with absolute certainty." The system also provides real-time inventory alerts and immediate notification when temperatures fluctuate out of specifications — allowing providers to worry less about their inventory and have more time to focus on patient care.

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HIPAA-Compliant Web-Based Survey Solution

SurveyMonkey, a provider of web-based survey solutions, now offers HIPAA-compliant features for all platinum customers at no extra cost. The company also has developed a business associate agreement (BAA) that contains the provisions required by HIPAA (includes the HITECH Act and related rules), making it simple and secure for covered entities to use SurveyMonkey's powerful tools to gather insights and make better decisions. SurveyMonkey will help covered entities meet their HIPAA obligations with the ability to easily enter into a BAA with SurveyMonkey (required of vendors or subcontractors who work with information protected by HIPAA); administrative, physical and technical safeguards consistent with HIPAA requirements; alert messages to remind customers of their HIPAA obligations and warn them when they perform sensitive operations on protected health information; logs of account activity; 30-minute session timeouts for idled accounts for added security; and the flexibility to negotiate a custom BAA for a nominal cost to fit more specialized compliance requirements. The upgraded features are designed to address new Department of Health and Human Services rules that went into effect on March 26 with a compliance deadline of September 23, including heightened financial penalties for organizations out of compliance.

SurveyMonkey, (650) 691-7321, www.surveymonkey.com

Breakthrough Tool Developed for MS

Researchers at Case Western Reserve University School of Medicine have developed a first-of-its-kind imaging tool to examine myelin damage in multiple sclerosis (MS). The new molecular marker, MeDAS, offers the first non-invasive visualization of myelin integrity of the entire spinal cord at the same time. Currently, a long lag exists between the onset of disease, physical symptoms and diagnosis via behavioral testing and magnetic resonance imaging. It is hoped that the tool will help physicians diagnose patients earlier, monitor the disease's progression and evaluate therapy efficacy. "While MS originates in the immune system, the damage occurs to the myelin structure of the central nerous system. Our discovery brings new hope to clinicians who may be able to make an accurate diagnosis and prognosis in as little as a few hours compared to months or even years," said Yanming Wang, PhD, senior author of the study and associate professor of radiology at Case Western. "Because of its shape and size, it is particularly difficult to directly detect myelin damage in the spinral cord; this is the first time we have been able to image its function at the molecular level." Created by Wang's laboratory, the MeDAS molecular probe works like a homing device. Injected into the body intravenouly, it is programmed to seek out and bind only to myelin in the central nervous system. A positron-emitting radioisotope label on the molecule allows a PET scanner to detect the targets and quantify their intensity and location. The data can then be reconstructed as an image.

Case Western Reserve University School of Medicine

BioResources

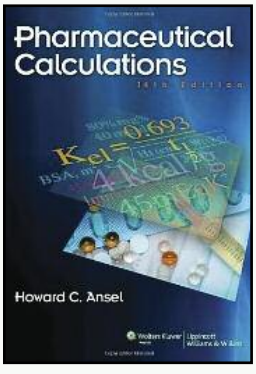
Recently released resources for the biopharmaceuticals marketplace.

Title 21 Code of Federal Regulations

Author: U.S. Food and Drug Administration

The new drugs/biologics-related Title 21 Code of Federal Regulations (CFR) five-volume set has been updated with the U.S. Food and Drug Administration (FDA) rules for drugs and biologics through April 1, 2013. The set, which will be available upon days of each volume's release, includes Parts 1-199 (FDA, General), Parts 200-299 (FDA, Drugs: General), Parts 300-499 (FDA, Drugs for Human Use), Parts 500-599 (FDA, Animal Drugs, Feeds and Related Products) and Parts 600-799 (FDA, Biologics; Cosmetics). Each volume includes the CFR-governing good manufacturing practices, Part 11 electronic records and signatures, drug enforcement policies, protection of human subjects, good laboratory practices, new drug approvals, biologics product licensing and more.

www.fdanews.com/store/product/detail?productId=21938&hittrk=13424&utm_source=MagnetMail&utm_medium=email&utm&utm_term=rrhodes@igliving.com&utm_content=BT2C513 - 13424 - 4/24/13 - RDR/RDD/MIRRORRDR&utm_campaign=Order New 2013 CFR Drugs/Biologics

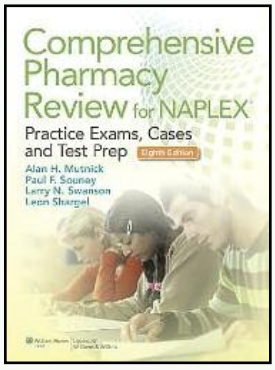


Pharmaceutical Calculations, 14th edition

Author: Howard C. Ansel

Pharmaceutical Calculations takes a step-by-step approach to calculations, making it easy for students to work through the problems and gain greater understanding of the underlying concepts. Its focus is on the fundamental principles and basic techniques involved in the application of the calculations needed for successful pharmacy practice. The 14th edition represents a thorough update of this textbook. Each chapter includes learning objectives that direct the student's focus and provide a basis for self-assessment following completion. Coverage includes new material in areas such as e-prescriptions, medication orders in nursing homes, hospice care, patient self-administration of analgesia, intravenous infusion rate calculations for the critical care patient, and patient conversions to alternative treatment plans.

www.lww.com/webapp/wcs/stores/servlet/product_Pharmaceutical-Calculations_11851_-1_12551_Prod-9781451120363



Comprehensive Pharmacy Review for NAPLEX: Practice Exams, Cases, and Test Prep

Authors: Alan H. Mutnick, Paul Souney, Larry N. Swanson, PharmD, FASHP, RPh, and Leon Shargel, PhD, RPh

This book is intended for anyone studying for the North American Pharmacists Licensure Examination (NAPLEX). In its 8th edition, the book deciphers the nuances of the test and provides authentic exercises and actionable strategies. Using two full-length tests, 32 brand-new patient cases and more than 200 practice calculations, students can challenge their understanding of current pharmacological practices and enhance their test-taking skills.

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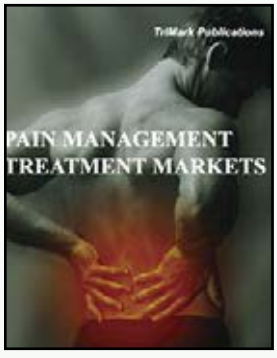

Pain Management Treatment Markets

Author: TriMark Publications

Pain Management Treatment Markets describes a particular set of drugs, analgesics, which are specifically used as therapeutics to control pain in the clinic. It focuses on the role of pain management drugs in clinical use and in drug development for acute pain, chronic pain, neuropathic path and nociceptive pain. The report discusses drug development and targeted therapeutics, as well as their use in clinical trials. New approaches meant to aid in development of drugs for therapeutic use are emphasized. The study also analyzes almost all of the major, specialty and emerging companies known to be marketing, manufacturing or developing pain management treatment products in the U.S. and worldwide. Additionally, this review provides detailed tables, charts and figures with past and projected sales data for the U.S., Europe and other geographic regions.

www.researchandmarkets.com/research/k3qxwk/pain_management

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IVIG Reimbursement Calculator

Product	Manufacturer	HCPCS	Medicare Reimbursement Rates* Rates are effective January 2014 through March 2014. ASP+6% (before sequestration)	ASP + 4.3%** (after sequestration)
BIVIGAM	Biotest Pharmaceuticals	J1556	$77.27	$76.03
CARIMUNE NF	CSL Behring	J1566	$73.69	$72.51
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$72.12	$70.96
GAMMAGARD LIQUID	Baxter	J1569	$78.68	$77.41
GAMMAGARD S/D (Low IgA)	Baxter	J1566	$73.69	$72.51
GAMMAKED	Kedrion	J1561	$79.54	$78.26
GAMMAPLEX	Bio Products Laboratory	J1557	$74.74	$73.54
GAMUNEX-C	Grifols	J1561	$79.54	$78.26
OCTAGAM	Octapharma	J1568	$61.23	$60.25
PRIVIGEN	CSL Behring	J1459	$73.45	$72.27

* Hospital outpatient and physician office settings

Calculate your reimbursement online at www.FFFenterprises.com.

** Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Biotest Pharmaceuticals	IVIG: PIDD	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PIDD, ITP	3 g, 6 g, 12 g
FLEBOGAMMA 5% & 10% DIF Liquid	Grifols	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g
GAMMAGARD LIQUID 10%	Baxter	IVIG: PIDD, MMN SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Baxter	IVIG: PIDD, ITP, CLL, KD	5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Laboratory	IVIG: PIDD, ITP	2.5 g, 5 g, 10 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PIDD	1 g, 2 g, 4 g, 10 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PIDD, ITP	5 g, 10 g, 20 g, 40 g

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

2013-2014 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code	Medicare Payment Allowance
Merck / CSL	AFLURIA (IIV3)	0.5 mL single-dose syringe	9 years and older*	90656	$12.398
		5.0 mL multi-dose vial		Q2035	$11.543
GlaxoSmithKline	FLUARIX (IIV3)	0.5 mL single-dose syringe	3 years and older	90656	$12.398
	FLUARIX QUADRIVALENT (IIV4)	0.5 mL single-dose syringe	3 years and older	90686	$19.409
	FLULAVAL (IIV3)	5.0 mL multi-dose vial	3 years and older	Q2036	$8.579
	FLULAVAL QUADRIVALENT (IIV4)	5.0 mL multi-dose vial	3 years and older	90688	$16.815
MedImmune	FLUMIST QUADRIVALENT (LAIV4)	0.2 mL single-use nasal spray	2–49 years	90672	$24.596
Novartis	FLUVIRIN (IIV3)	0.5 mL single-dose syringe	4 years and older	90656	$12.398
		5.0 mL multi-dose vial		Q2037	$14.963
	FLUCELVAX (ccIIV3)	0.5 mL single-dose syringe	18 years and older	90661	$20.663
Protein Sciences	FLUBLOK (RIV3)	0.5 mL single-dose vial	18–49 years	90673	$36.480
Sanofi Pasteur	FLUZONE (IIV3)	0.25 mL single-dose syringe	6–35 months	90655	$17.243
		0.5 mL single-dose syringe	3 years and older	90656	$12.398
		0.5 mL single-dose vial	3 years and older	90656	$12.398
		5.0 mL multi-dose vial	6–35 months	90657	$6.022
		5.0 mL multi-dose vial	3 years and older	Q2038	$12.044
	FLUZONE QUADRIVALENT (IIV4)	0.25 mL single-dose syringe	6–35 months	90685	$23.228
		0.5 mL single-dose syringe	3 years and older	90686	$19.409
		0.5 mL single-dose vial	3 years and older	90686	$19.409
	FLUZONE HIGH-DOSE (IIV3)	0.5 mL single-dose syringe	65 years and older	90662	$31.823
	FLUZONE INTRADERMAL (IIV3)	0.1 mL single-dose microinjection system	18–64 years	90654	$18.918

IIV3 Egg-based trivalent inactivated injectable
ccIIV3 Cell culture-based trivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

* Age indication per package insert is ≥5 years; however, the Advisory Committee on Immunization Practices recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5-8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine. Afluria may be used in persons aged ≥9 years.

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Coagulation Factor IX (Human), marketed as AlphaNine® SD
Factor IX Complex, marketed as Profilnine® SD
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- Hepatitis B Immune Globulin (Human), marketed as HyperHEP B® S/D

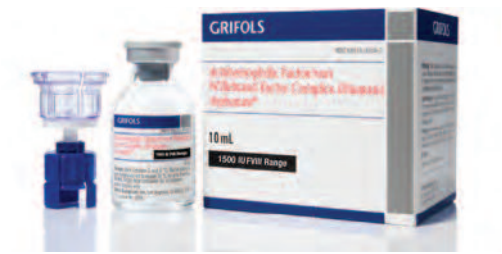
Grifols also provides operational solutions for compounding areas in pharmacy and diagnostic instrumentation, reagents, software and related products for the clinical laboratory.

Learn more about how Grifols can meet your hospital's needs at **www.grifols.com**

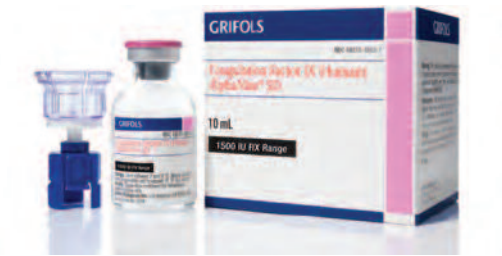
1. Marketing Research Bureau data, June 2012

Grifols provides the following product choices:

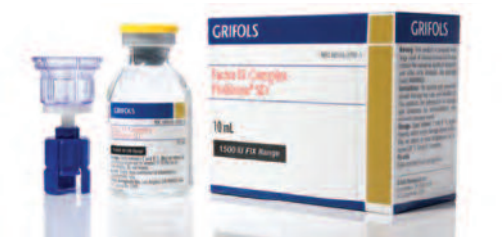
Alphanate®
Antihemophilic Factor/von Willebrand Factor Complex (Human)



AlphaNine® SD
Coagulation Factor IX (Human)



Profilnine® SD
Factor IX Complex



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