October 2013

BioSupply Trends

Special Focus: INNOVATION

Anti-Aging Medicine

The Science Behind Life Extension

Reducing the Threat of Hospital-Acquired Infections

Medical Informatics to Improve Healthcare Quality

Expanding the Pharmacist's Role

Myths & Facts: Celiac Disease

Universal Flu Vaccine — Page 48

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

October 2013

Features

Special Focus: Innovation

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

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

Up Front

BioTrends Watch

BioFocus

BioSources

Innovation: The Path of Progress

JUST A CENTURY ago, most people could never have imagined that today we would almost double their average life expectancy of 47 years. Or, that we would have computers that could connect wirelessly to the other side of the world, allowing us to share massive amounts of data with just a push of a button. Or, that we would have modern acute-care hospitals all over the world employing medical advances that save millions of lives every year. But, these incredible innovations achieved in such a relatively short time are just a few of innumerable examples of science's path to alter the field of medicine.

For instance, a fear of death and the undesirability of looking old spurred scientists to begin exploring the causes of aging in the 1930s and 1940s. Since then, we've come a long way in our understanding of not just how the body ages, but how to slow the aging process and increase life spans. In our article "From Here to Immortality: Anti-Aging Medicine," we look at how regenerative medicine may one day rejuvenate an individual to live to the age of 130; how there soon may be a new crop of drugs to significantly extend human life spans; and how stem cell transplants show promise to reverse the aging process.

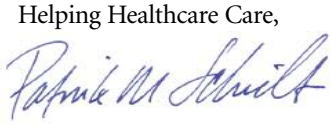
Of course, scientific progress relies upon our ability to share data. Computers and the Internet have opened up astonishing amounts of information to the world. Still, it's how we are able to use that information that will enable further progress. Right now, the new field of medical informatics is exploring the many ways in which data can be collected and organized to improve healthcare quality. Our article "Medical Informatics: Mining Data to Improve Healthcare" highlights how metadata registries and organizations like the Agency for Healthcare Research and Quality are standardizing data supplied by healthcare organizations all over the U.S. to help improve patient care, prevent medical errors and reduce costs. This revolutionary way of mining data has opened up an all-new medical specialty that is predicted to create thousands of jobs in the coming years.

While innovative progress typically results in hard-won successes, a byproduct of these advances can be adverse consequences. Such is the case for today's acute-care hospitals, urgent care clinics and many other types of healthcare facilities that have become breeding grounds for an increasing number of hospital-acquired infections (HAIs). With Centers for Disease Control and Prevention (CDC) estimating that some two million people contract an HAI each year, it is a serious issue. Our article "The Serious Threat of HAIs" takes a look at these types of infections and how to combat them. Through innovative efforts, more than 11,000 medical facilities in the U.S. are being tracked for infections, and CDC has implemented detailed and multi-pronged plans that have already resulted in lowered rates of infection.

Just as it was impossible for previous generations to predict today's scientific and technological advances, we are similarly challenged when looking to the future. But, as these articles illustrate, the path to progress begins with innovation. And, in the past 100 years, we've made amazing strides.

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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HHS Launches Video Contest with Young Invincibles

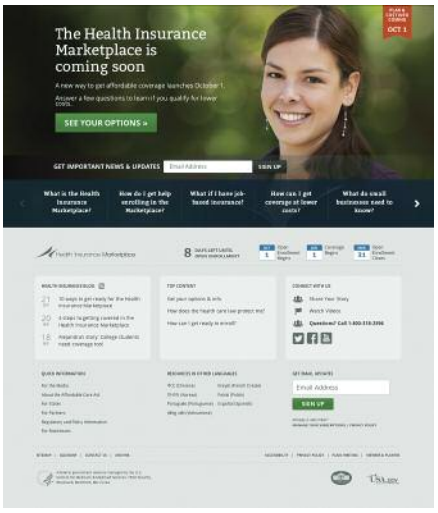
The Department of Health and Human Services (HHS) and Young Invincibles have launched a video contest in an effort to inform young people about health insurance coverage and new options under the Affordable Care Act. People can submit entries and vote for their favorite videos at www.healthyyoungamerica.org.

"The millennial generation has always been a creative generation, which is why we are so pleased to partner with HHS in launching the Healthy Young America video contest," said Aaron Smith, co-founder and executive director of Young Invincibles. "Educating millions of young people about the changes coming this year is vital to helping them achieve economic security. This competition will engage young people by reaching them through a medium that they prefer to use when sharing and receiving content."

Young Invincibles is in the midst of a nationwide campaign designed to inform young adults about coming changes and new options. The campaign includes a healthcare "train the trainers" promotional program to help community leaders be informed about new changes. A website with frequently asked questions and a mobile app to help consumers learn their options, find local healthcare services and get information on enrollment events this fall also are included in the campaign.

Young people also can access a variety of online tools through HealthCare.gov, and they can count on in-person help to get answers to their questions to help them enroll beginning Oct. 1. They can use the site to join web chats or call (800) 318-2596 to get help from a trained customer service representative. "Health insurance is out of reach for millions of young people today because it costs too much or isn't offered through a job," said HHS Secretary Kathleen Sebelius. "Soon, the health insurance marketplace will give uninsured young people the opportunity to enroll in affordable health insurance, and the Healthy Young America video contest will help them tell their stories to other young people." ❖

Health Insurance Marketplace Tools Unveiled



In June, the Obama administration launched the consumer-focused HealthCare.gov website and the 24-hour call center in an effort to help Americans successfully navigate the Health Insurance Marketplace. The new educational tools are designed to aid consumers in selecting the best health coverage options and prepare them for open enrollment beginning Oct. 1.

The website continued to add user functionality through the summer so that, by October, consumers could create accounts, complete online applications and shop for qualified health insurance plans. The website also will feature social media integration, sharable content, engagement destinations for consumers to find more information, and web chat functionality to support additional inquiries.

Consumers can access HealthCare.gov from their desktops, smartphones and other mobile devices. Spanish speakers can visit CuidadoDeSalud.gov to view and access the same information available on the English website. In addition to English and Spanish, the call center will provide assistance in more than 150 languages through an interpretation and translation service. ❖

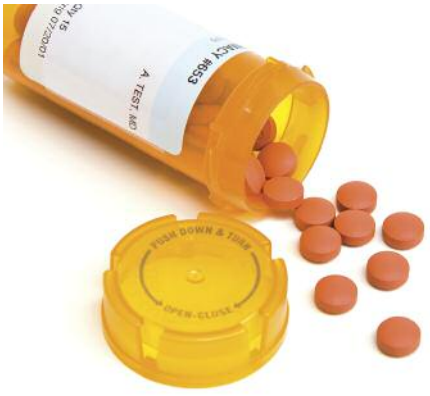
NGA Publishes Report on Maternal and Child Health Services Reforms

According to the National Governors Association (NGA) report titled *Effect of Provider Payment Reforms on Maternal and Child Health Services*, states are vigorously pursuing policies and initiatives that are intended to reduce healthcare costs while enhancing outcomes and access to care for children and pregnant women. While most healthcare reform efforts do not specifically target maternal and child health services, the initiatives identified in this report have the potential to reduce costs while improving outcomes for pregnant women and children. The report examines state initiatives such as paying for good outcomes and bundling payments to providers to ensure coordination of care at a reasonable cost. ❖

Health Centers Given $150M to Help Uninsured Americans Gain Coverage

Approximately 1,200 health centers and 9,000 service delivery sites nationwide will receive $150 million in new funding from the Obama administration to enable them to help more uninsured Americans enroll in health coverage plans made available under the Affordable Care Act. The funding will allow health centers to hire new staff, improve the skills of current employees and sponsor community outreach activities and events. They also will help clients determine their eligibility, understand their coverage options, and offer one-on-one enrollment assistance for qualified health plans, Medicaid, the Children's Health Insurance Program and the new Health Insurance Marketplace. The funding was issued by the Health Resources and Services Administration and aligns with the efforts of the Centers for Medicare and Medicaid Service navigator program. ❖

New Law to Battle Pharmaceutical Counterfeiting



The U.S. House of Representatives has passed the Safeguarding America's Pharmaceuticals Act. Introduced by Rep. Bob Latta of Ohio, the law enforces new regulations on the network of businesses that distribute, handle, produce and dispense medicines. The law aims to increase patient safety by establishing a national standard of determining requirements for manufacturers, wholesale distributors, pharmacies and repackagers based on changes in ownership. In addition, the law will make it mandatory for all companies that are part of the supply chain to provide notifications to state and federal regulators whenever a product is deemed unacceptable for distribution.

The current system of state and federal guidelines has compromised the security of the national distribution supply chain, allowing counterfeit medications to reach some of the sickest patients. This law proposes to create a clear, united process between the U.S. Food and Drug Administration and stakeholders to study additional ways to safeguard the pharmaceutical supply chain, eliminate repetitive regulations and create trust in the prescription drug marketplace. ❖

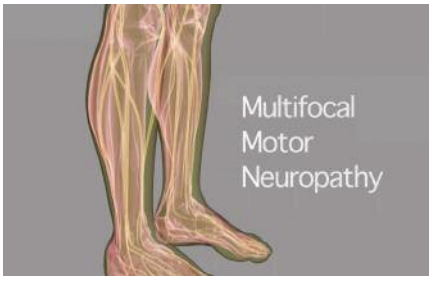
HHS Grants $32M to Enroll Children in Health Insurance

In July, the U.S. Department of Health and Human Services awarded $32 million in grants to help identify and enroll uninsured children who are eligible for Medicaid and the Children's Health Insurance Program (CHIP). The Connecting Kids to Coverage Outreach and Enrollment Grants were presented to 41 community health centers, nonprofit organizations, academic groups and state agencies.

The grants, which are part of the $140 million included in the Affordable Care Act and the Children's Health Insurance Program Reauthorization Act, were awarded in five categories: engaging schools in outreach, enrollment and retention activities; reducing health coverage inconsistencies by connecting with subgroups of children who are less likely to be insured; streamlining enrollment for consumers participating in other public benefit programs; improving application assistance resources to provide dependable Medicaid and CHIP enrollment and renewal services in local communities; and training communities to deliver assistance to families and help them understand the new application and enrollment system. ❖

Public Service Announcement

PSA Launched to Raise Awareness for MMN



The Neuropathy Action Foundation (NAF) and the GBS/CIDP Foundation International have launched a joint nationwide campaign to raise awareness of multifocal motor neuropathy (MMN), a rare and incurable neurological condition in which multiple motor nerves are attacked by the immune system. The national campaign will include an educational MMN-specific brochure, as well as a public service announcement (PSA) to help patients and medical professionals identify, treat and manage the progressive condition.

"Multifocal motor neuropathy is a serious but treatable condition where early and accurate diagnosis is critical to preserving the livelihood of those touched by the disease. The ability to control the progression of MMN is directly related to how quickly the disease is correctly diagnosed," said NAF founder Dominick Spatafora. "I was originally diagnosed with ALS and told that I had only three to five years to live. It took more than a year before I was correctly diagnosed with MMN and began receiving the life-sustaining IVIG [intravenous immune globulin] treatments that continue to help me 10 years later."

Although MMN is a rare disease — likely affecting no more than one to two in 100,000 people — it can cause serious disability if not correctly diagnosed. Most MMN patients are originally misdiagnosed multiple times before correctly being diagnosed with MMN, and the correct diagnosis may take years. To view the PSA, go to www.youtube.com/watch?v=OjOg_YIwhcE&feature=plcp&nomobile=1. ❖

Medicines

CDC Updates VariZIG Use Recommendations

The Centers for Disease Control and Prevention (CDC) has updated its recommendations for the use of VariZIG, which are now harmonized with the American Academy of Pediatrics. VariZIG is a varicella zoster immune globulin preparation manufactured by Cangene Corp. for use in the U.S. for postexposure prophylaxis of varicella for persons at high risk for severe disease who lack evidence of immunity to varicella and for whom varicella vaccine is contraindicated. VariZIG is currently approved by the U.S. Food and Drug Administration for administration as soon as possible following varicella-zoster virus exposure, ideally within 96 hours (four days) for greatest effectiveness. However, CDC now recommends administration of VariZIG as soon as possible after exposure to the varicella-zoster virus and within 10 days. Limited experience from outside the U.S. with use of other immune globulin products with high levels of anti-varicella-zoster virus antibodies suggested that, compared with administration of the immune globulins within four days of exposure, administration greater than four days and up to 10 days after exposure resulted in comparable incidence of varicella and attenuation of disease. One study indicated an increase in varicella incidence with increasing time between exposure and administration of ZIG, but disease was attenuated in all cases.

CDC also has revised the patient groups recommended by the Advisory Committee on Immunization Practices to receive VariZIG. Patient groups recommended to receive VariZIG include immunocompromised patients without evidence of immunity; newborn infants whose mothers have signs and symptoms of varicella around the time of delivery (five days before to two days after); hospitalized premature infants born at greater than or equal to 28 weeks of gestation whose mothers do not have evidence of immunity to varicella; hospitalized premature infants born at less than 28 weeks of gestation or who weigh less than or equal to 1,000 grams at birth, regardless of their mothers' evidence of immunity to varicella; and pregnant women without evidence of immunity. Now, CDC extends the period of eligibility for previously recommended premature infants from exposures to varicella-zoster virus during the neonatal period to exposures that occur during the entire period for which they require hospital care for their prematurity.

VariZIG can be ordered from the exclusive U.S. distributor, FFF Enterprises Inc., at (800) 843-7477 or online at www.fffenterprises.com. ❖

Medicines

FDA Launches Secure Supply Chain Pilot Program

The U.S. Food and Drug Administration (FDA) has launched the Secure Supply Chain Pilot Program (SSCPP) to enable qualified firms to expedite the importation of active pharmaceutical ingredients and finished drugs into the United States. The goal of the program is to enable FDA to focus its imports surveillance resources on preventing the entry of high-risk drugs that are the most likely to compromise the quality and safety of the U.S. drug supply. Participating firms will demonstrate a commitment to securing their drug supply chains in the Customs-Trade Partnership Against Terrorism (C-TPAT).

The SSCPP, administered by FDA's Center for Drug Evaluation and Research and Office of Regulatory Affairs, is a voluntary program open to 100 qualified applicants. Each firm accepted to participate in the program will be allowed to have up to five drugs subject to expedited import entry review. Firms that apply must meet certain criteria that include, but are not limited to: 1) The applicant must be the NDA/ANDA sponsor or the foreign manufacturer of the imported finished drug product or active pharmaceutical ingredient. 2) Foreign drug manufacturers and U.S. establishments receiving drugs must comply with good manufacturing practices and also be in compliance with the registration and listing requirements outlined in sections 510(i) and 510(j) of the Federal Food, Drug and Cosmetic Act. 3) Applicants must have a validated secure supply chain protocol per the U.S. Customs and Border Protection's C-TPAT program as either C-TPAT Tier II or Tier III.

FDA began accepting applications on Sept. 26 and will continue through Dec. 31. The pilot program will run from February 2014 through February 2016. To view the application for the program, go to www.fda.gov/cder/fedreg/fda-3676.pdf. To view the displayed federal register notice, go to www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-N-0656-N.pdf. ❖

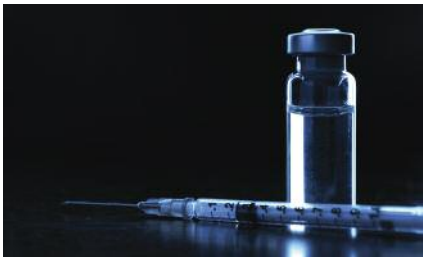
Did You Know?

"On June 21, the world's first human infection of H6N1, a low-pathogenic avian influenza virus that exists commonly in birds, was reported on the island Xinhua in Taiwan. The 20-year-old patient had not left Taiwan recently and had not had any recent contact with birds. Four of the 26 people the patient has had close contact with have shown flu-like symptoms, but possible H6N1 infections were ruled out by tests."

— Center for Infectious Disease Research and Policy

Vaccines

FDA Approves Two New Quadrivalent Vaccines



The U.S. Food and Drug Administration has approved two new quadrivalent influenza vaccines (IIV4s). In June, FDA approved Sanofi Pasteur's new Fluzone Quadrivalent for use in children ages 6 months and older, adolescents and adults. It is the first and only IIV4 option for children as young as 6 months. The pediatric dose is available in 0.25 mL preservative-free prefilled syringes for children ages 6 months to 35 months. For individuals 36 months and older, it is available in 0.05 mL one-dose vials and 0.5 mL prefilled syringes. In clinical trials, the most common local and systemic adverse reactions were pain, erythema and swelling at the vaccination site; myalgia; malaise; headache; and fever. Some young children also experienced irritability, crying and drowsiness.

In August, FDA approved Glaxo SmithKline's Flulaval Quadrivalent for the prevention of influenza caused by types A and B strains in adults and children ages 3 years and older. Flulaval Quadrivalent will be available in 5 mL multi-dose vials containing 10 0.5 mL doses. This is GlaxoSmithKline's second intramuscular IIV4 approved by FDA.

These vaccines join two other available IIV4s: Fluarix Quadrivalent (GlaxoSmithKline), approved for adults and children ages 3 years and older, and FluMist (MedImmune), approved for adults and children 2 years through 49 years. ❖

Research

Study Reveals Barriers to Flu Vaccine for Pregnant Women

A recent study conducted to evaluate barriers to pregnant women's uptake of the influenza vaccine found that the decline in vaccination among this population was due to lower levels of knowledge and unfavorable attitudes regarding the vaccine's safety and efficacy. In the study, 88 women completed a survey designed to assess participant demographics, knowledge, beliefs, attitudes and general experiences with seasonal and 2009 novel H1N1 influenza. The researchers then assessed patient characteristics and vaccine uptake. Women who correctly answered more than 75 percent of knowledge questions regarding influenza were significantly more likely to accept the influenza vaccine. Conversely, patients who declined the vaccine were more likely to hold false beliefs such as perceiving that the vaccine was not protective and that they were not at risk for influenza. The study was published in the June 12 edition of *Vaccine*. ❖

Vaccines

New Vaccine Developed for Foot and Mouth Disease

The first vaccine to protect children against the enterovirus 71, or EV71, that causes the common and sometimes deadly hand, foot and mouth disease (HFMD) has been developed by Chinese scientists at Beijing Vigoo Biological. A trial of the vaccine took place at four sites across China involving 10,245 babies and children aged 6 months to 35 months who were randomly assigned to receive two doses of the vaccine or two doses of a placebo. The results, which were published in the May 28 issue of *The Lancet*, showed that the vaccine was 90 percent protective against EV71-associated HFMD, with 80.4 percent protection for at least 12 months. Until now, there have been no effective vaccines against EV71.

Since the EV71 virus was discovered in 1969, it has caused major outbreaks of HFMD around the world, affecting mostly children. In recent years, large increases in the number of cases have occurred in Asia. A large outbreak of HFMD infected approximately 35,000 people and killed 17 in China's Hunan province in June 2012.

The EV71 and several other viruses, one of which is called coxsackievirus A 16, which is often found circulating with EV71, can cause HFMD. The researchers cautioned that there was no evidence this vaccine would cross-protect against that virus. ❖

Medicines

New Vial Size Approved for CSL Behring's Hizentra

The U.S. Food and Drug Administration has approved a 10 g (50 mL) vial size for Hizentra, immune globulin subcutaneous (human), manufactured by CSL Behring. Hizentra is the only 20 percent subcutaneous immune globulin therapy, which keeps serum immunoglobulin G (IgG) levels consistent week to week to help protect people with primary immunodeficiency against infections. The new vial size, which became available in the U.S. in October, will reduce the number of vials that patients must use when higher doses are required, thus increasing administration efficiency and reducing complexity of care. In addition to the 10 g vial, Hizentra is also available in 1 g (5 mL), 2 g (10 mL) and 4 g (20 mL) vials.

"CSL Behring remains dedicated to providing every patient with options that will enhance his or her treatment experience," said Lynne Powell, senior vice president, North America Commercial Operations. "The availability of Hizentra in a 10 g vial will reduce vial preparation for infusion, therefore saving time for both patients and their caregivers." ❖

Vaccine Update

Novavax Inc. announced positive preclinical data for its virus-like particle (VLP) vaccine candidate against A(H7N9) influenza. The study examined the immunogenicity and efficacy of two doses of its A(H7N9) VLP vaccine candidate against a lethal wild-type challenge mouse model. Three control groups included Novavax' non-homologous A(H7N3) VLP vaccine candidate, its A(H5N1) VLP vaccine candidate and a placebo. All vaccine candidates were administered with or without Iscomatrix, a saponin-based adjuvant. The data were published online in the peer-reviewed journal *Vaccine*. ❖

For life's sensitive moments…

Grifols is committed to the prevention of Rh hemolytic disease of the newborn (HDN) by providing HyperRHO® S/D Full Dose (Rh_0[D] immune globulin [human])

HyperRHO S/D Full Dose provides the critical protection needed[1]

- It contains high titers of Rh_0(D) immune globulin antibodies to optimize protection and reduce the potentially life-threatening risk of HDN[1]
- It is the first Rh_0(D) immune globulin product with FDA-approved labeling for removal of pathogenic prions that may cause TSE* disease in humans[1]

Partnering with healthcare professionals at this sensitive time of your patients' lives

In fulfilling our commitment to you and your patients, we at Grifols are proud to deliver exceptional customer service and ensure product availability when your patients need it most.

Product information[1]

Product	NDC#	Description	Size
HyperRHO S/D Full Dose	13533-631-02	Single-dose Prefilled Syringe	1500 IU

For intramuscular administration only.

To learn more, visit www.hypermunes.com.

Meet Kim† and baby.

- Rh-negative, first-time mother-to-be with an Rh-positive baby
- Mother needs immediate protection
- Mother received HyperRHO S/D Full Dose at week 28 and later within 72 hours of full-term delivery

Important Safety Information

HyperRHO® S/D Full Dose (Rh_0[D] immune globulin [human]) is indicated for prevention of Rh hemolytic disease of the newborn (HDN) and the prevention of isoimmunization in Rh_0(D) negative individuals who have been transfused with Rh_0(D) positive red blood cells.

HyperRHO S/D Full Dose is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Never administer HyperRHO S/D Full Doses intravenously. Inject only intramuscularly. Never administer to the neonate.

Rh_0(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. 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.

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive DU test result. If there is any doubt about the mother's Rh type, she should be given Rh_0(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 red blood cells are present in the mother's circulation, more than a single dose of HyperRHO 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 symptoms.

Administration of live virus vaccines (eg, MMR) should be deferred for approximately 3 months after Rh_0(D) Immune Globulin (Human) administration.

HyperRHO S/D Full Doses should be given in pregnant women only if clearly needed because animal reproduction studies have not been conducted.

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.

Elevated bilirubin levels have been reported in some individuals receiving multiple doses of Rh_0(D) Immune Globulin (Human) following mismatched transfusions. This is believed to be due to a relatively rapid rate of foreign red cell destruction.

Please see brief summary of HyperRHO S/D Full Dose complete Prescribing Information on adjacent page.

HyperRHO® S/D
Rh_0(D) Immune Globulin (Human)

*Human TSEs (transmissible spongiform encephalopathies) are a group of neurodegenerative diseases related to mad cow disease.
†Not an actual patient.

Reference: 1. HyperRHO® S/D Full Dose (Rh_0[D] immune globulin [human]) [package insert]. Research Triangle Park, NC: Grifols Inc; 2012.

June 2013 HY24-0613

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Grifols Customer Service 1.800.243.4153

GRIFOLS

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.

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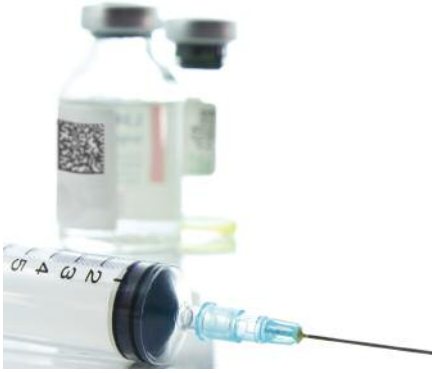
Vaccines

New Vaccine Barcodes Enhance Safety

Using two-dimensional (2D) barcodes on vaccine product labels would enhance the safety of the U.S. immunization system and save more than $300 million by 2023, according to a study by researchers at RTI International and the U.S. Centers for Disease Control and Prevention. The study, published in the June issue of *Vaccine*, found that implementing 2D barcodes on vaccines will enhance the accuracy of the data, lower the burden of documenting immunizations and increase the probability of being able to locate a patient should a vaccine be recalled. The study also showed that between 2011 and 2023, the net economic benefits from switching vaccines to using 2D barcodes were forecasted to be between $310 million and $334 million.

Immunization providers are required by the National Childhood Vaccine Injury Act to record the vaccine and lot information for vaccines administered to patients. Although product labels have had linear barcodes, those barcodes only contained the National Drug Code. Providers still had to record the lot number and expiration date by hand — essential information in the event of a product recall or locating patients having received recalled lots — but that information is often missing or inaccurate in records. The 2D barcodes can contain the National Drug Code, expiration date and lot number in a symbol small enough to fit on a label appearing on a 0.5 mL vial. It can be scanned to verify it matches doctors' orders and automatically populate records with the required product information. And, in



conjunction with electronic health records, 2D barcodes make it easier to enter immunizations into registries.

The researchers surveyed more than 3,600 primary care providers and found that 60 percent of pediatric practices, 54 percent of family medicine practices and 39 percent of health departments would use the 2D barcode. More indicated they would use the barcode if they used electronic health records. ❖

Vaccines

Quadrivalent VLP Vaccine Achieves Phase II Trial Endpoints

Novovax Inc.'s quadrivalent seasonal influenza virus-like particle (VLP) vaccine demonstrated the company's Phase II clinical trial's primary endpoint of safety and immunogenicity of three ascending dose levels. The VLP vaccine demonstrated immunogenicity against all four viral strains based on Hemagglutination Inhibition Assay (HAI) responses at day 21, was well-tolerated with no vaccine-related serious adverse events observed, and reactogenicity was considered acceptable.

The VLP vaccine also exceeded protocol design expectations by fulfilling the study's secondary endpoint to fulfill the U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research criteria for accelerated approval. In adult populations under 65 years of age, the VLP vaccine fulfilled the FDA seroprotection criterion at the lower 95 percent confidence bound for all four viral strains included. It also demonstrated the potential to fulfill the FDA seroconversion criterion by demonstrating greater than or equal to 40 percent seroconversion against three of four viral strains. However, despite fulfilling the seroprotection criterion, the fourth virus (B/Brisbane/60/08) failed to meet the seroconversion criterion. But the inclusion of a fourth viral strain in the quadrivalent formulation did not have a significant impact on the immunogenic performance of the other three strains when compared with a trivalent VLP formulation.

An additional secondary endpoint to evaluate the immunogenicity of the VLP vaccine at various dose levels in comparison with a licensed trivalent inactivated vaccine (IIV3) produced in eggs also fulfilled the FDA criteria for seroprotection and seroconversion for each of the included three strains. In general, the comparator IIV3 reached higher levels of HAI than the company's VLP quadrivalent vaccine.

Additional safety and immune response follow-up is continuing through six months post-treatment. ❖

From Here to Immortality: Anti-Aging Medicine

Anti-aging medicine is a $5 billion industry. Despite its critics, researchers are discovering that interventions designed to turn back time may prove to be more science than fiction.

By Trudie Mitschang

The symptoms are disturbing. Weight gain, muscle aches, fatigue and joint stiffness. Some experience hearing loss and diminished eyesight. In time, both memory and libido will lapse, while sagging skin and incontinence may also become problematic. It is a malady that begins in one's late 40s, and currently 100 percent of baby boomers suffer from it. No one is immune and left untreated; it always leads to death. A frightening new disease, virus or plague? No, it's simply a fact of life, and it's called aging.

The mythical fountain of youth has long been the subject of folklore, and although it is both natural and inevitable, human beings have been resisting the aging process for centuries. The early Greeks were the first to theorize that aging was a disease resulting from an imbalance of internal fluids. From there, alchemists, shamans and snake-oil salesmen have all preyed on the desperate and the gullible, promising to turn back the clock — for a price, of course.

A Brief History of Anti-Aging Medicine

In the 1930s and 1940s, scientists began taking a more serious and academic look at the root causes of aging. Common theories of the day included the idea that genetic mutations cause physiological deterioration. Then, in 1961, anatomist Leonard Hayflick (dubbed the father of modern anti-aging research) proved that cells do in fact have a finite life and that in laboratory tests, cells from older people die more quickly than those from younger people. This discovery gave rise to the theory that humans have an internal "clock" that could possibly be reset in order to slow the aging process.

In the last 30 years, theories of aging have come and gone. In a paper presented to the Los Angeles Gerontology Research Group at the UCLA School of Medicine, Dr. L. Stephen Coles, MD, PhD, identified 25 current theories of aging, with most falling into one of two schools of thought: the school of chance and the school of grand design.[1] The first theorizes that wear and tear is the main cause of aging; in a nutshell, the body simply wears out due to use, abuse and deterioration. The second theory states that after a certain period of time, our bodies trigger a genetic code that slows repairs. Support for this theory can be seen in simpler organisms in nature like lobsters, coral and sponges, which show no signs of aging at all. The fact that they show no signs of deterioration suggests that some evolutionary change must have occurred as creatures became more complex.

In 1993, a landmark study by Cynthia Kenyon, PhD, at the University of California, San Francisco, found that mutations in a single gene could double the life span of Caenorhabditis elegans, a type of small worm often used in genetic studies. This one single finding provided the first step in proving the gene expression theory of aging and sparked a wave of research for extending human life span.[2]

Shifting Attitudes Fuel a Booming Industry

The notion that aging requires treatment is based on a belief that becoming old is both undesirable and unattractive. In the last several decades, aging has become synonymous with deterioration, while youth is increasingly revered and admired. Anti-aging medicine is a relatively new but thriving field driven by a baby-boomer generation fighting to preserve its "forever young" façade. According to the market research firm Global Industry Analysts, the boomer-fueled consumer base will push the U.S. market for anti-aging products from about $80 billion now to more than $114 billion by 2015.[3]

In the last 30 years, theories of aging have come and gone.

So, what exactly is anti-aging medicine? Traditional doctors such as endocrinologists and geriatricians are specifically trained to treat age-related conditions, but anti-aging as a medical specialty is not currently recognized by the American Board of Medical Specialties, meaning doctors can't officially be board-certified in it. But, that has not stopped the field from founding its own professional society, the American Academy of Anti-Aging Medicine (A4M). Founded in 1992, A4M boasts some 24,000 members worldwide and offers a certificate in anti-aging medicine, available to any MD.[3] In its mission statement, the academy says the disabilities associated with normal aging "are caused by physiological dysfunction which in many cases are ameliorable to medical treatment, such that the human life span can be increased."

Anti-aging enthusiasts such as the A4M contend that life spans can be prolonged through interventions such as hormone replacement therapy and dietary supplements, while critics say many anti-aging interventions are ineffective or possibly even harmful. Mainstream organizations such as the National Institute on Aging recommend consumer skepticism when it comes to anti-aging products and treatments. "Our culture places great value on staying young, but aging is normal," the institute says. "Despite claims about pills or treatments that lead to endless youth, no treatments have been proven to slow or reverse the aging process."[3]

But one of A4M's co-founders, Robert Goldman, a doctor of osteopathic medicine, contends that much of the resistance to the anti-aging movement comes from sectors of the health and pharmaceutical industries that feel threatened financially by

the increased use of products like nutritional supplements. "It all has to do with who's controlling the dollars," he says.[3]

Is Aging Optional?

It is one thing to slow the progression of aging, but it is another thing entirely to begin rejuvenating life at the cellular level. According to one renowned British gerontologist: "Aging is emphatically not an inescapable destiny." Aubrey de Grey, author of the book *Ending Aging*, became interested in the field of regenerative medicine more than a decade ago. De Grey's work is influential and far-reaching; his institute has established a scientific prize for extending the lives of mice by rejuvenation or other means. The Methuselah Foundation provides cash rewards to researchers who surpass past performance regarding the life span of mice; the highest performance to date is 1,819 days in January 2012 (life spans for mice in the wild average one year).[4]

In the last several decades, aging has become synonymous with deterioration, while youth is increasingly revered and admired.

But critics argue de Grey's theories are radical; he believes that within 30 years, it may be possible to rejuvenate a 50-year-old individual to such a youthful condition that he/she will live to the age of 130. He also contends that comparable rejuvenation technology for a mouse may be discovered within 10 years. His theories are based on the idea that the key to rejuvenation is the repair of seven distinct kinds of damage that represent aging: cell loss; cell senescence; extracellular protein cross-linking; nuclear DNA mutations; mitochondrial DNA mutations; and the accumulation of "garbage" inside, as well as outside, cells. After extensive research, de Grey developed a seven-step plan designed to curb the identified specific organic damages linked to age dubbed Strategies for Engineered Negligible Senescence (SENS),[4] even co-founding a foundation by the same name. The foundation, headquartered in Mountain View, Calif., describes itself as the "only nonprofit currently prioritizing a regenerative medicine approach to the diseases of aging."

At the heart of its efforts, SENS funds the research and development of new classes of medicines called "rejuvenation biotechnologies." Rejuvenation biotechnologies are targeted therapies that apply the principles of regenerative medicine across the entire scope of the damage of aging. In other words, instead of merely slowing down the accumulation of aging damage in our tissues, rejuvenation biotechnologies will remove, repair or replace the damaged cellular and molecular machinery. This means that with every round of therapy, a person's eyes, heart, arteries and bones will not just suffer less ongoing degradation of their structures, but will actually become more youthful and healthier in their structure and function, as the fine cellular and molecular order of these and other tissues are progressively restored to their youthful integrity. SENS Research Foundation is actively funding and performing research to develop, promote and ensure widespread access to these innovations, promoting the training of young scientists in this new approach, and disseminating rejuvenation research into health research and biotechnology institutes and biotechnology nationwide. Its stated goal? To "reimagine aging and open up lives of vigor and health set free from the gravitational pull of time."[5]

Breakthrough Studies Show Promise

Can a pill that slows the aging process really be in the pharmaceutical pipeline? Some researchers say yes. Based on numerous studies, a growing consensus states that we are closer than ever to an innovative crop of drugs that will significantly extend human life spans. One recent report says the first could debut in just five years.

Landmark work led by an Australian researcher and published in the March 8, 2013, issue of *Science* demonstrates that a single anti-aging enzyme in the body can be targeted, with the potential to prevent age-related diseases and extend life spans. The paper shows all of the 117 drugs tested work on the single enzyme through a common mechanism. This means that a whole new class of anti-aging drugs is now viable, which could ultimately prevent cancer, Alzheimer's disease and type 2 diabetes.[6]

The target enzyme, SIRT1, is switched on naturally by calorie restriction and exercise, but it can also be enhanced through activators. The most common naturally occurring activator is resveratrol, which is found in small quantities in red wine, but synthetic activators with much stronger activity are in development. "Ultimately, these drugs would treat one disease, but unlike drugs of today, they would prevent 20 others," says the lead author of the paper, Professor David Sinclair from UNSW Medicine, who is based at Harvard University. "In effect, they would slow aging."[6]

The drugs in development will be administered orally and/or topically. While any drug would be strictly prescribed for certain conditions, Sinclair suggests that one day they

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Together, we can protect the safety of our prescription drugs.

could be taken orally as a preventative. This would be in much the same way as statin drugs are commonly prescribed to prevent, instead of simply treat, cardiovascular disease.[6]

Gene therapy is another exciting field of study. A team of scientists led by Ronald DePinho at Harvard University has managed to control the aging process by targeting specialized structures at the tips of chromosomes called telomeres. When the researchers genetically engineered mice to have short telomeres, mice aged prematurely. When they used gene therapy to lengthen telomeres, the reverse happened. Aging, infertile mice with shriveled testes and diminished cognitive abilities began to revive. DePinho has estimated that, overall, the mice went from being what was essentially ages 80 to 90 in human years to the equivalent of middle age in the course of the experiment.[7]

In other studies, scientists have found that feeding aging mice rapamycin — an immunosuppressant that is used to prevent organ rejection after transplants — can extend the life span of mice significantly. Researchers say the drug seems to improve the functioning of mitochondria, structures that generate power for cells. Previous research has shown that mitochondria dysfunction is involved in numerous diseases of aging.[7]

The Stem Cell Connection

In early May, a team of Harvard Stem Cell Institute scientists announced the discovery of a protein that circulates in blood that causes old, enlarged hearts to revert to a more youthful size and functionality. The study, performed with mice, could lay a foundation for a new approach to therapy for a common form of heart failure that strikes the elderly. "The change was unbelievably obvious," says Dr. Richard T. Lee, a cardiologist at Brigham and Women's Hospital and one of the leaders of the study. "Usually, we do quite sophisticated quantitative analyses of hearts and the shapes of the cells and things like that. ... You could see what happened from the very first experiment."[8]

Can a pill that slows the aging process really be in the pharmaceutical pipeline?

In another recent study, researchers at the University of Pittsburgh Medical Center genetically altered mice to make them age faster, making them old and weak in a span of 17 days. The scientists then injected the mice with stem cell-like cells taken from the muscle of young, healthy mice, reversing the aging process. The rapidly aging mice lived up to three times longer, dying after 66 days, rather than 28 days. The cell

injection also appeared to make the animals healthier, improving their muscle strength and brain blood flow. Dr. Laura Niedernhofer, one of the study's authors, says even though the injection of young cells didn't necessarily rebuild the bodies of the mice, it did seem to improve their body health. "The young stem cells seem to secrete something that is quite beneficial," says Niedernhofer.[9]

A recent slew of popular books and websites claim that individuals can calculate their "real" age by answering a series of questions.

And, in Georgia, researchers have shown they can reverse the aging process for human adult stem cells, which are responsible for helping old or damaged tissues regenerate. The findings could lead to medical treatments that may repair a host of ailments that occur because of tissue damage as people age. A research group led by the Buck Institute for Research on Aging and the Georgia Institute of Technology conducted the study in cell culture, which appears in the Sept. 1, 2011, edition of the journal *Cell Cycle*. "We demonstrated that we were able to reverse the process of aging for human adult stem cells by intervening with the activity of non-protein-coding RNAs originated from genomic regions once dismissed as nonfunctional 'genomic junk,'" says Victoria Lunyak, associate professor at the Buck Institute for Research on Aging.[10]

The "Real Age" Factor

A recent slew of popular books and websites claim that individuals can calculate their "real" age by answering a series of questions regarding their own habits, health history, chronic conditions, weight, blood pressure, family history, etc. Participants can then determine if their biological age is older or younger than the age on their driver license.

Dr. Michael Roizen is an internist and anesthesiologist and co-founder of RealAge Inc., a consumer health media company and provider of personalized health-management tools, as well as chairman of the RealAge scientific advisory board. He serves as chief wellness officer and chairman of the Wellness Institute at the Cleveland Clinic. Roizen's popular RealAge website spotlights 149 factors, from weight, cholesterol and blood pressure, to drinking and driving, talking on a cell phone while driving and using birth control, that all influence longevity. While these types of surveys are more anecdotal than scientific, proponents say they can have a positive influence on anyone hoping to add years to their life — or life to their years.

"There are actually 190 factors that influence aging, but 149 that you can change," Roizen says, noting that while people cannot change the genes they inherit from their parents, they can change the activity of those genes. Roizen refers to research looking at the glutathione S-transferase mu 1 (GSTM1) gene, which he says fights breast and prostate cancer. For example, the authors of one study found that by eating four servings a week of broccoli, men reduced their risk of prostate cancer because of the vegetable's effect on the anticancer gene.

Besides dietary changes, Roizen claims lifestyle choices and personal habits can also boost longevity, with habits like regular exercise and flossing topping the must-do list. "Virtually anyone can live to age 90 with the quality of life that they had at age 45," says Roizen. "San Francisco is built on fault lines. Whether it survives a magnitude 2.9 or 8.9 earthquake without damage depends on its building codes and how rigorously they're enforced. We're all built with fault lines in our genes, but whether we live to 90 or 100 with the quality of life of someone who is 45, or whether we die at 68 living with a disability and [at the real age] of someone who is 90 depends on our choices."[11] ❖

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References

1. Why Do We Age? The Current Theories. HealthAliciousNess.com. Accessed at www.healthaliciousness.com/articles/why-do-we-age.php.
2. Ullis, K. *Anti-Aging Medicine: History and Theories*. Accessed at www.enotalone.com/health/5476.html.
3. Crary, D. Boomers Will Be Pumping Billions Into Anti-Aging Industry. *The Huffington Post*, Aug. 20, 2011. Accessed at www.huffingtonpost.com/2011/08/20/boomers-anti-aging-industry_n_932109.html.
4. Best, B. Aubrey de Grey, PHD: An Exclusive Interview with the Renowned Biogerontologist. *Life Extension Magazine*, February 2006. Accessed at www.lef.org/magazine/mag2006/feb2006_profile_01.htm.
5. SENS Research Foundation. Introduction to SENS Research. Accessed at www.sens.org/about.
6. Anti-Aging Drug Breakthrough. *Science Daily*, Mar. 8, 2013. Accessed at www.sciencedaily.com/releases/2013/03/130308111312.htm.
7. Voiland, A. The Hunt for An Anti-Aging Pill Is On. *U.S. News & World Report Health*, Mar. 14, 2012. Accessed at health.usnews.com/health-news/articles/2012/05/14/the-hunt-for-an-anti-aging-pill-is-on?page=2.
8. Johnson, CY. Science in Mind: Harvard Stem Cell Researchers Find Protein that Rejuvenates Aging Mouse Hearts. Boston.com, May 9, 2013. Accessed at www.boston.com/news/science/blogs/science-in-mind/2013/05/09/harvard-stem-cell-researchers-find-protein-that-rejuvenates-aging-mouse-hearts/kqC6SzTO9hMAvSpiqiyB3O/blog.html.
9. Gann, C. Stem Cell Shots Reverse Aging in Mice. ABC News, Jan. 3, 2013. Accessed at abcnews.go.com/Health/stem-cells-turn-back-clock-aging-mice/story?id=15280185.
10. Scientists Turn Back the Clock on Adult Stem Cells Aging. GeorgiaTech.com, Sep. 20, 2011. Accessed at www.gatech.edu/newsroom/release.html?nid=70083.
11. Roizen, M. 12 Ways to Reduce Your Real Age. *Success Magazine*. Accessed at www.success.com/articles/608-12-ways-to-reduce-your-real-age.

SUPERBUGS:

Reducing the Serious Threat of HAIs

Hospital-acquired infections remain a deadly threat, but the Centers for Disease Control and Prevention in partnership with other healthcare agencies and professionals are working to lower the rates of HAIs with some degree of success.

By Jim Trageser

Ask friends, family and colleagues for their list of the most important technological advances of the 20th century, and you're likely to get answers ranging from powered flight to the computer and telecommunications. But the modern acute-care hospital — while it may not be on many people's lists — has had as large an impact on our society, and on tens of millions of individual lives, as any of the above important advances.

The development of the modern hospital is so ubiquitous to contemporary life that it is often overlooked, lost in its commonality and taken for granted. From "Dr. Kildare" to "Marcus Welby, MD," "ER" and "Grey's Anatomy," popular culture has enshrined today's hospital as a kind of secular cathedral — impressive but also often invisible. Until we need it.

Before the 1900s, hospitals had a horrible but likely accurate reputation as bastions of filth and disease — as places the poor went to die and the rich avoided (treating their family members at home).[1] Predating many of our discoveries about microbiology, 19th century and earlier hospitals concentrated the sick in wards that lacked modern antiseptic measures, resulting in the unintended effect of creating highly fertile breeding grounds for infectious disease. Even in the 20th century, the Spanish flu killed more young men than the ongoing World War I — mostly from the ability of the flu virus to spread quickly among closely compacted populations in military barracks and hospital wards.

Twentieth-century advances in immunization, antibiotics and disinfectants, and in the education and professionalism of

physicians and nurses, helped change both the perceptions and reality of hospitals. At the same time, rapid developments in surgical techniques made treating patients at home impractical — even for the rich — meaning that many life-saving procedures could only be accessed at a centralized facility with specialized equipment and sterile conditions. These factors all combined to turn our modern hospitals into places of hope and healing.

Today, these hard-won advances in the efficacy and reputation of hospitals are being threatened by a troubling, stubborn bubble in the number of infections acquired in hospitals, urgent care centers, long-term care centers and other healthcare facilities. They are all prone to serving as home to an increasing array of hospital-aquired infections (HAIs) that endanger the health and even lives of the patients being treated in them.

About 5 percent of all hospital patients in the U.S. have an HAI at any given time.

The threat of HAIs, also known as superbugs, has become so serious that, in 2008, the U.S. Department of Health and Human Services (HHS) empaneled the multi-agency Federal Steering Committee for the Prevention of HAIs.[2] The committee is chaired by Dr. Don Wright, MD, deputy assistant secretary for health for HHS' Office of Disease Prevention and Health Promotion.

How Big a Problem?

According to Wright, about 5 percent of all hospital patients in the U.S. have an HAI at any given time.[3] The Centers for Disease Control and Prevention (CDC) estimates that, in 2002, 1.7 million Americans contracted an HAI.[4] That number is believed to have risen to about two million per year by 2009.[5] The European Centre for Disease Prevention and Control estimated earlier this year that three million Europeans contract an HAI each year.[6]

And the mortality rate of HAIs is fairly high. In the U.S., CDC estimates that some 99,000 deaths per year are at least partially contributed to by an HAI.[7] That's almost 5 percent of those who contract an HAI. The European counterpart estimates some 25,000 deaths per year are due to HAIs. (It is not clear that the U.S. and European centers use the same methods in measuring the culpability of HAI in patient mortality, as the above numbers would result in a European mortality rate less than one-fifth that in the U.S.)

While the numbers alone are staggering — millions of people in Europe and the U.S. acquiring a secondary infection while being treated at a medical facility each year — the economic cost is equally sobering. A study prepared for CDC calculated that HAIs in 2007 cost U.S. hospitals roughly $30 billion to treat.[8]

Considering that the Centers for Medicare and Medicaid has been excluding treatment of preventable HAIs from reimbursement eligibility, and that private insurers are beginning to follow suit,[9] the financial burden of treating HAIs is likely to increasingly fall on hospitals and other healthcare facilities. And, the above price tag does not factor in the cost of malpractice claims and litigation filed by patients and their families who feel their HAI was preventable — only the immediate cost of treatment.

Gathering Information

Over the past few years, CDC has been tracking HAIs in minute detail, collecting precise information on these infections, including which organisms cause them and how the infection invaded the body.[10] This information gathering has happened under the auspices of two separate but parallel programs: the National Healthcare Safety Network (NHSN)[11] and the Emerging Infections Program (EIP).[12] The NHSN tracks HAI reports from more than 11,000 medical facilities in the U.S., while the EIP gathers data from 10 state health departments and academic institutions.

Among the microbes most responsible are more than a dozen bacteria and viruses being tracked by CDC's HAI program:[13]

- Acinetobacter
- Burkholderia cepacia
- Clostridium difficile (C. difficile)
- Clostridium sordellii
- Enterobacteriaceae (carbapenem-resistance)
- Hepatitis
- Human immunodeficiency virus (HIV)
- Influenza
- Klebsiella
- Methicillin-resistant Staphylococcus aureus
- Mycobacterium abscessus
- Norovirus
- Pseudomonas aeruginosa
- Staphylococcus aureus
- Tuberculosis
- Vancomycin-intermediate Staphylococcus aureus and vancomycin-resistant Staphylococcus aureus
- Vancomycin-resistant Enterococci

A number of these (Acinetobacter, Burkholderia cepacia, Pseudomonas aeruginosa) are common in everyday environments (naturally present in soil and water), posing little risk to healthy individuals. But in a hospital setting with patients whose weakened immune systems are unable to respond, these normally benign bacteria can become deadly.

The same is true of bacteria associated with the human digestive tract (escherichia coli [E. coli], Klebsiella, Enteroccocci), where they normally do their job without causing us any health problems. Remove them from our intestines and put them near patients with compromised immune systems, and they are a serious danger.[13]

CDC has been tracking HAIs in minute detail, collecting precise information on these infections.

For the most part, these particular bacteria can still be effectively treated by current antibiotics. The resistant strains on the list are the ones garnering the alarming headlines in the popular media — for the very sobering reason that our ability to fight them is limited. And, these strains exist almost exclusively in healthcare facilities.

The major entry points tracked by CDC are catheters, surgical incisions and ventilators.[14] The infection types designated by CDC are based on both the entry point and the part of the body that becomes infected:[15]

- Surgical site infection
- Central line-associated bloodstream infection
- Catheter-associated urinary tract infection
- Ventilator-associated pneumonia

Looking more closely at HAIs, certain agents are associated with certain designated infections. For instance, cather-associated urinary tract infections are most commonly caused by Enterobacteriaceae (carbapenem-resistance), Klebsiella or vancomycin-resistant Staphylococcus aureus.[14]

Not Just Hospitals

One of the byproducts of the dramatic rise in healthcare costs of the past few decades has been the growth in the number of alternatives to a traditional acute-treatment hospital. From urgent-care clinics offering a lower-cost option to the emergency room to outpatient surgical facilities, long-term residential nursing care and dialysis centers, there are numerous examples of nonhospital medical facilities that serve the same role as a ward in a full-service hospital.

Not surprisingly, these medical facilities are seeing the same challenge from HAIs as are the hospitals they complement and compete with. In fact, CDC's HAI-prevention program even includes dental facilities.[16] Any place where invasive procedures compromise the body's defense against hostile organisms is capable of spreading HAIs.

Fighting Back

Using the solid body of statistics it has compiled on HAIs, CDC and other health organizations and professionals have already begun devising strategies to prevent these infections — and develop more effective treatments for those patients who are infected.

With more than 11,000 medical facilities being tracked for HAIs in this country alone, CDC admits that a 100 percent eradication is not a realistic goal at this time. But even the government's 2009 target goal of a 40 percent reduction by the end of September 2013 (compared with 2010 infection rates) would mean tens of thousands fewer premature deaths each year in the United States alone.

The government-led HAI task force issued its *National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination* in 2009, which included the above target goal. That plan provides detailed and multipronged plans that are geared specifically to the types of facilities, the bacteria or viruses causing the infection, and the most common methods of transmission. It is organized into three main sections: acute-care hospitals, outpatient facilities and long-term care facilities.[17] Many of the recommendations are surprisingly low-tech and common-sense: Are your staff members washing their hands as often as they should? Are instruments being properly sterilized?[18]

Consistency in following both legal guidelines and proven best practices remains the most effective method in preventing HAIs. Properly trained medical professionals know how to disinfect an examination or operating room, and how to follow established parameters to reduce infection risk. It's doing it properly over and over again, for every patient every day without ever growing lax or careless, that is the greatest challenge — the weakest link in the prevention chain.

To help administrators follow through on meeting this difficult human challenge of consistently following protocols to prevent HAIs, CDC has numerous materials available in a centralized online location: www.cdc.gov/HAI/prevent/prevention.html. There are brochures and one sheets, flyers and posters, almost all available in PDF format that can be downloaded and printed out. While these are no substitute for professional training materials and curriculum, they are a good starting point to ensure staff are clear on their obligations and the best methods for meeting them.

Making Progress

CDC reports that some transmission methods are already seeing lowering rates of infection. By 2010, central line-associated bloodstream (CLAB) infection rates had dropped 18 percent from two years earlier.[19] CDC attributed the drop to better and more consistent implementation of best practices by staff at

the 1,500 hospitals that took part in the study the results were based on. A year later, the rate of CLAB infections had dropped even further.[20]

A smaller program involving just seven hospitals from around the U.S. that focused on reducing surgical site infections during colorectal surgeries managed to achieve a 32 percent reduction over an 18-month period.[21] Another benefit of avoiding infections is that the patients needed shorter hospital stays before going home to continue their recovery.

A promising front in the battle against HAIs is the use of copper in more surfaces in hospital equipment. The May issue of the journal *Infection Control and Hospital Epidemiology* included a study on copper in hospital settings, showing HAI infection rate reductions of up to 58 percent when copper is used in place of other metals and existing preventive techniques are followed.[22]

One of the challenges facing public health officials trying to both encourage improvements in HAI prevention while also accurately measuring them is that hospital and other healthcare facilities are only all too human — and there have been several studies showing both wide discrepancies in reported infection rates among similar facilities[23] and suggestions that reported rates of some HAIs may be artificially lowered due to expectations of success.[24]

Looking Ahead

As the lead agency in the effort to reduce the human cost of HAIs, CDC continues to invest in research in multiple disciplines to try to improve technology and techniques in battling HAIs. Among the current research efforts:

• Working on new tests to make detection of HAI-linked microorganisms quicker and more accurate

• Investigating the biology of vancomycin-resistant Staphylococcus aureus

• Studying new methods of ensuring the sanitation of water supplies in healthcare facilities[25]

CDC and its partners, both private and public, are continuing their efforts to accurately measure HAIs, improve the training and performance of healthcare professionals to lower the incidence of secondary infections acquired at healthcare facilities, and develop new treatments to cure those patients who do become infected.

The results so far are promising, if incomplete. But the attention brought to bear on the issue should ensure that preventable infections become rarer in the years to come. ❖

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References

1. Vallgarda S. Who went to a general hospital in the eighteenth and nineteenth centuries in Copenhagen? *European Journal of Public Health*, Vol. 9, 1999, No. 2. Accessed at eurpub.oxfordjournals.org/content/9/2/97.full.pdf.
2. U.S. Department of Health and Human Services. Organizational Structure of the HHS Initiative for the Prevention of Health Care-Associated Infections. Accessed at www.hhs.gov/ash/initiatives/hai/orgstructure/index.html.
3. U.S. Department of Health and Human Services. Release of the 2013 National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination, Jun. 4, 2013. Accessed at content.govdelivery.com/accounts/USHHS/bulletins/7de8d4.
4. Centers for Disease Control and Prevention. Healthcare-Associated Infections: The Burden. Accessed at www.cdc.gov/HAI/burden.html.
5. Stone PW. Economic burden of healthcare-associated infections: an American perspective. Columbia University Center for Health Policy, 2009. Accessed at cumc.columbia.edu/studies/pnice/documents/Economic-Burden-of-HAIs-Expert-Review.pdf.
6. Kelland K. Three million Europeans catch infections in hospital annually. Reuters, Jul. 4, 2013. Accessed at www.reuters.com/article/2013/07/04/us-europe-hospitals-infections-idUSBRE96309820130704.
7. Pollack A. Rising Threat of Infections Unfazed by Antibiotics. *New York Times*, Feb. 26, 2010. Accessed at www.nytimes.com/2010/02/27/business/27germ.html?em=&adxnnl=1&adxnnlx=1267412412-yP2bfl/3pu4+g34XVmluJA&_r=0.
8. Centers for Disease Control and Prevention. The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention. Accessed at www.cdc.gov/hai/pdfs/hai/scott_costpaper.pdf.
9. Lexington Insurance. Healthcare-Associated Infections: The Emerging Risk of Liability. 2010 Risk Management/Patient Safety Seminar. Accessed at www.chartisinsurance.com/ncglobalweb/internet/US/en/files/Chartis_Healthcare_Associated_Infections_tcm295-413858.pdf.
10. Centers for Disease Control and Prevention. Monitoring Healthcare-Associated Infections. Accessed at www.cdc.gov/HAI/surveillance/index.html.
11. Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN). Accessed at www.cdc.gov/nhsn.
12. Centers for Disease Control and Prevention. Emerging Infections Program. Accessed at www.cdc.gov/HAI/eip.
13. Centers for Diease Control and Prevention. Diseases and Organisms in Healthcare Settings. Accessed at www.cdc.gov/HAI/organisms/organisms.html.
14. Centers for Disease Control and Prevention. Types of Healthcare-Associated Infections. Accessed at www.cdc.gov/HAI/infectionTypes.html.
15. Premier Inc. What Are Healthcare-Associated Infections (HAIs)? Accessed at www.premierinc.com/safety/topics/HAI/#WhatAreHAIs.
16. Centers for Disease Control and Prevention. Preventing Healthcare-Associated infections. Accessed at www.cdc.gov/HAI/prevent/prevention.html#dent.
17. Centers for Disease Control and Prevention. National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination. Accessed at www.hhs.gov/ash/initiatives/hai/actionplan/index.html.
18. Centers for Disease Control and Prevention. Top CDC Recommendations to Prevent Healthcare-Associated Infections. Accessed at www.cdc.gov/HAI/prevent/top-cdc-recs-prevent-hai.html.
19. O'Reilly KB. Central-line infections declining, CDC reports. *American Medical News*, Jun. 14, 2010. Accessed at www.amednews.com/article/20100614/profession/306149949/2.
20. Centers for Disease Control and Prevention. 2011 National and State Healthcare-Associated Infections Standardized Infection Ratio Report. Accessed at www.cdc.gov/hai/national-annual-sir.
21. O'Reilly KB. Simple steps prevent surgical site infections. American Medical News, Dec. 12, 2012. Accessed at www.amednews.com/article/20121212/profession/121219941/8.
22. Brown T. Healthcare-acquired infections reduced by copper surfaces. *Medscape News Today*, Apr. 12, 2013. Accessed at www.medscape.com/viewarticle/782461.
23. Michetti CP, Fakhry SM, Ferguson PL, et al. Ventilator-associated pneumonia rates at major trauma centers compared with a national benchmark: a multi-institutional study of the AAST. *J Trauma Acute Care Surg* 2012 May;72(5):1165-73. Accessed at www.ncbi.nlm.nih.gov/pubmed/22673241.
24. Klompas M. Is a ventilator-associated pneumonia rate of zero really possible? *Curr Opin Infect Dis* 2012 Apr;25(2):176-82. Accessed at www.ncbi.nlm.nih.gov/pubmed/22248978.
25. Centers for Disease Control and Prevention. Healthcare-Associated Infections (HAIs): Research. Accessed at www.cdc.gov/HAI/research/research.html.

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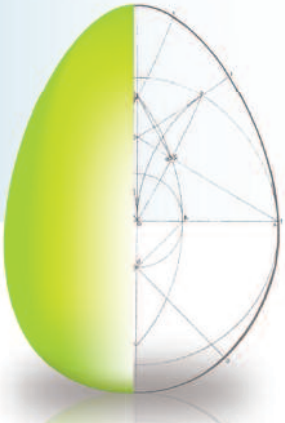

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Important Safety Information

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

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

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

Monitor patient vital signs throughout infusion of Privigen. In cases of severe hypersensitivity or anaphylactic reactions, discontinue administration and institute appropriate medical treatment. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have occurred in patients with risk factors; consider baseline assessment of blood viscosity for those at risk of hyperviscosity. Patients could experience increased serum viscosity, hyperproteinemia or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur (most often with high doses and/or rapid IVIg infusion).

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

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

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

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

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

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

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

1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA
www.CSLBehring-us.com www.Privigen.com PVG10-11-0014a 6/2012

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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Medical Informatics

Mining and organizing data to improve healthcare quality is quickly becoming a reality, and it is big business.

By Amy Scanlin, MS

Improving healthcare at a reduced cost has long been a goal of the medical community. One way of accomplishing this is with medical informatics, or the use of vast quantities of data aggregated into usable searches, organized results and, in turn, improved procedures. In the coming years, medical informatics is anticipated to be a breakthrough strategy yielding higher-quality healthcare that can help to improve patient care, prevent medical errors and reduce costs — all with a query and a push of a button. And, it has never been more exciting and, in some cases, closer with the increased usage of electronic health records (EHR), the ability to pull data from health plans and health systems, the growing area of genomics and more.

The latest push for medical informatics came about when the *2012 National Healthcare Quality and Disparities Report* (published each year as mandated by Congress to focus on

national trends in the quality of healthcare provided to the American people) indicated that healthcare quality and access are suboptimal, particularly for minorities and low-income individuals. In response, the U.S. Department of Health and Human Services called for an action plan. That plan, in part, is the need for improved data access for the underserved (which is often incomplete or collected in too low a quantity to be meaningful) to improve healthcare quality.[1]

But, for medical informatics to work, policy decision makers, researchers and end users need to determine how best to collect, store, compare and improve upon digital data collection, analytics and reporting. Some challenges of how best to implement policy for maximizing comparative effectiveness research include data quality, data representation, data completeness, data timeliness, governance, technology, privacy, sustainability and issues of workforce development.[2]

Data Collection

The term "data" and what it encompasses has undergone an evolution, according to the American Medical Informatics Association (AMIA). The field of genomics, the methods of physician, device and hospital reporting, and even individual self-reporting, all factor into the very broad term that researchers are using to improve health outcomes of patients. What's challenging, though, is that there is no single national healthcare database or clearinghouse of information from which to sort. Instead, data is collected in a variety of ways and in a variety of databases, and each provides estimates for the populations for which they serve. For instance, data is collected via health plans, health systems, inpatient, outpatient and emergency departments, and others.

To help solve this challenge, metadata registries are now being used. Metadata registries are a way of collecting data without collecting the actual data itself. They store data elements that include both semantics (the meaning of a data element with precise definitions) and representations (the definition of how data is represented in a specific format).

One such registry is the Agency for Healthcare Research and Quality's (AHRQ) U.S. Health Information Knowledgebase (USHIK). Prior to the formation of USHIK, a major barrier to EHRs was a lack of standardization of codes, even for things as simple as gender, marital status and race. Getting that content right, so that researchers looking at data could compare apples to apples, was of the utmost importance. The creation of USHIK was a joint effort by the Centers for Medicare and Medicaid Services (CMS), as well as other agencies, with CMS taking the lead, working to meld the informatics initiative with the standards of HIPAA to find the right vocabulary that makes content understandable at both ends of the transmission process.

Determinations had to be made for which aspects would be addressed in hammering out the patient safety common format standards, such as "their definitions, their names, how they are represented (their code sets), the vocabularies in which they come, the base standard from which they are derived, and the organization that maintains the particular vocabulary or the code set such as for ICD-10 in the United States," explains Michael Fitzmaurice, PhD, senior science adviser for information technology at AHRQ. (In the U.S. , the National Center for Health Statistics maintains the ICD-10 code set.)

In the coming years, medical informatics is anticipated to be a breakthrough strategy yielding higher-quality healthcare that can help to improve patient care, prevent medical errors and reduce costs.

While data is not input directly into USHIK, says Fitzmaurice, there are "several organizations that input intellectual property about the data into the database, and [there are] a handful of states that input information about their data into USHIK." These include standards developing organizations, federal and state organizations, specific harmonizing initiatives and others.[3] "We have found a unique way of meeting those who provide intellectual property head on in a way that satisfies their needs," adds Fitzmaurice. And, the voluntary reporting of their data is protected in court so "while it is proprietary data, we do have good success in obtaining the data dictionaries. They have freely given us the data dictionaries, and we put them into USHIK. They could pull their data out at any time if we didn't treat it right. But, we do good things with the data, and so far they like it. It is mutually beneficial. Researchers can turn out robust findings."

Once data is collected, it has to be analyzed through algorithms to provide information on health trends, readmissions, healthcare costs and any number of subjects a user would like to search. "Congress charged AHRQ to look at patient safety, and we focused on hospital reporting standards in common formats, what questions were being asked and what answers

were supplied, and how they should be coded," explains Fitzmaurice. "We supplied the formats, hospitals provided the patient safety data, and we combined them looking for commonalities — kind of a 'daisy chain.'" They then put the name, definition and attributes about the data into USHIK so the user can view side-by-side comparisons to see how they compare or how they don't compare. This is particularly useful to researchers because, when combining the actual data, they need to know that the data means the same thing — particularly the same thing as the concepts they are investigating.

Applications of Data Use

There are many examples of how researchers, administrators and clinicians are making use of the information contained in health informatics databases for improved patient care and improving costs.

A newer area of study for AHRQ is the Multiple Chronic Care Research Network (MCCRN), which is looking at patients with multiple comorbidities.

USHIK. Those who rely on USHIK include EHR vendors, state public health departments, physicians, researchers, developers and policymakers. One example of how USHIK is being used is with meaningful use stage II (which must be met by EHR vendors in order to continue to participate in the Medicare and Medicaid EHR Incentive Programs). USHIK contains the clinical quality measures, how they are calculated, the data elements used in the calculation, and the codes that the data elements can use such as ICD-9 or ICD-10 codes and SNOMED code for something like diagnostics, says Fitzmaurice. With this, an EHR vendor may want to compare what is in the EHR data dictionary with what needs to be in the data dictionary to produce the Medicare and Medicaid clinical quality measures for the incentive payment program. Or, there could be a vendor that may want to compare what is required for certification so that their EHR can produce the clinical quality measures for meaningful use stage II. Those vendors "can come to USHIK as a one-stop shop and get the clinical quality measures," explains Fitzmaurice.

AHRQ Common Formats. The Quality Assessment and Performance Improvement (QAPI) Act of 2005 was implemented to require hospitals to track adverse patient events. However, recent reports by the HHS Office of the Inspector General (OIG) indicated that hospitals fail to identify most adverse events. In response, the OIG recommended that AHRQ and CMS help hospitals improve their ability to track adverse patient safety events by disseminating information on AHRQ's Common Formats. The AHRQ Common Formats define a systematic process for reporting adverse events, near misses and unsafe conditions, and allow a hospital to report harm from all causes. While hospital use of the AHRQ Common Formats is voluntary, CMS recently stated in a memo that hospitals that use them and are adept at the analysis that they permit will be in a better position to meet the QAPI requirements.[4]

Advanced analytics for analyzing hospital readmission rates. Hospital readmission rates became an even more critical financial hurdle to overcome in 2012 when the government began withholding 1 percent of base Medicare reimbursement from hospitals with excessive readmissions, and again in 2013, when the penalty climbed to 2 percent, with an expected 3 percent in 2014. But, according to a report by Health Data Management, "by leveraging advanced analytics, organizations can identify which conditions are the best candidates for quality improvement initiatives." The analytics "would take into account the cost of the interventions required to have an impact on readmission rates compared with the total revenue reductions that a hospital would experience if readmission rates land them in the bottom quartile, subjecting the hospital to financial penalties as prescribed by the Affordable Care Act."

Looking at the cost of interventions that could prevent readmissions and comparing those with the cost of the readmissions, as well as the penalties assessed, analysts can determine which conditions have the highest readmission rates, for whom and which interventions can be implemented with success and, in turn, where their resources can be best spent for the greatest return in reducing readmission rates — a kind of proactive readmission approach.[5]

Multiple Chronic Care Research Network. A newer area of study for AHRQ is the Multiple Chronic Care Research Network (MCCRN), which is looking at patients with multiple comorbidities. "It's a big initiative across HHS," says Richard Ricciardi, PhD, RN, health scientist at AHRQ. "We are looking at ways to improve quality, the patient experience and value. Two-thirds of all claims data are related to multiple chronic conditions (MCC). These are high-utilizers with high costs."

Questions that AHRQ is seeking answers to are: How is it best to treat these patients? Which is the most important

disease to start with? How will the medications interact with each other? And, "How can we best approach this as a team?" explains Ricciardi. Working with patients with MCCs is a complex process, not linear, and clinicians need to know "how best to improve outcomes for the patients, improve their quality of life and, in layman's terms, get the biggest bang for the buck."

In 2010, AHRQ began looking at comparative effectiveness and infrastructure studies to develop guidance to facilitate a research network. One question they had was how they could build the infrastructure so that research can be better conducted. They paired databases in an effort to enable more exploratory research, and linked research papers to collectively start putting it all together.

MCCRN looks at various tools, including information technology, for improving patient outcomes. One example is a study by Dr. Henry Fisher, at the Denver Health and Hospital Authority, who conducted an interventional study on bidirectional text messaging for diabetic patients. Patients were reminded by text message to send in their data, and the data they sent in via text was reported to their healthcare team. Many patients found that it helped them to keep their diabetes under control because they felt like someone cared and was reaching out to them. "It's a good reminder that mobile technology has potential to improve outcomes," says Ricciardi.

Another area under review is building databases for dual-eligibles or those with mental health issues as part of their comorbidity, and how the healthcare team can help these patients stay on track with taking their medications and other health improvement interventions.

MONAHRQ. MONAHRQ, or My Own Network, powered by AHRQ Learning Network, is a free tool that uses hospital discharge data for measurements and comparisons by hospitals, communities, counties and states. Researchers can look at quality of care for emergency room, inpatient and outpatient settings; quality ratings and avoidable hospital stays by specific conditions; procedures and hospitals; as well as financials of specific hospitals or by county. Users also can compare data with results found in Hospital Compare, a website hosted by CMS.

"MONAHRQ uses state discharge data sets, which are pretty uniform across the states as far as the date, procedure and diagnosis code," says Susan Schow, Pathways to Excellence program director at the Maine Health Management Coalition. Schow was previously at the Maine Health Data Organization and was instrumental in getting MONAHRQ up and running in the state. "It is great! You can take all the data sets and query, without having any special data language, program or query code. It is wonderful for small programs with limited funds but great needs. It can drill down to a very discrete level."

Not only does MONAHRQ offer functionality today, but that functionality can power new ideas and better capabilities. Just thinking off the cuff, Schow adds that MONAHRQ would be useful as a tool for verifying required event reporting. "The more people who are aware of this, the more widely it can be used to help inform on healthcare — to make policy," she explains. "It's free to anyone — researchers, policymakers, hospitals — and it is great because you don't have to pay to analyze data."

Certainly, a big question when it comes to data mining is how to protect patients' privacy when their personal information is collected with the data.

"It became very clear when we saw the functionality of these data streams that we needed to transform ourselves," says Karynlee Harrington, executive director at the Maine Health Data Organization. "We need to take that cost data and expand it to join with quality data. We want to go a lot further than we originally planned! I have a vision of taking the MONAHRQ cost information and querying it down to hospital information in a geographic area, and then query the utilization out of it."

Patient Privacy

Certainly, a big question when it comes to data mining is how to protect patients' privacy when their personal information is collected with the data. In many states, patients have an all-or-nothing opt-in or opt-out option of providing their health information to data warehouses. In other states, there is more control on what information is shared and how.

A small study conducted at the Weill Cornell Medical College in New York found that while most patients support the idea of sharing health information, "78 percent would prefer to explicitly approve the sharing of all types of information, and most prefer restricting information by clinician (83 percent), visit (81 percent) or information type (88 percent)." Another study found that 70 percent of patients are either somewhat or very concerned about the privacy of their medical information in light of the new health information exchanges (HIEs). Even physicians who feel that HIEs are valuable tools are concerned about privacy. As more states launch HIEs, the issue of privacy and how best to protect it will be extremely

important. Federal and state agencies will need to address their privacy policies and technical standards.[6]

"Privacy is a big issue," says Dave Page, PhD, a professor in the Department of Biostatistics and Medical Informatics and the Department of Computer Science at the University of Wisconsin at Madison. Through medical informatics, "we are combining data from many different sites, and each hospital and provider owes [its] patients privacy." While data is de-identified, in some cases, "noise" is added or data is changed just slightly to further protect patient data. "If you jiggle the data a little bit, then you can't distinguish one patient from another," explains Page. In bigger models, the idea is "differential privacy," or the idea of de-identifying patients and only asking certain questions of the database so that the data would not be significantly different whether or not that person was included. Page cites the well-known case in which Harvard professor and researcher LaTanya Sweeney was able to re-identify Massachusetts Governor William Weld from his anonymous hospital discharge records as a high-profile example of the importance of ensuring the privacy of data.

Clinical Informatics Subspecialty

The schooling of health informatics is big business in and of itself. In 2011, the American Board of Medical Specialties approved clinical informatics as a board-certified medical subspecialty. The informatics specialist is able to determine which data will be most useful in clinical decision-making, and how that data should be delivered to physicians. In an article published in *American Medical News*, AMIA's Board of Director Chair Nancy Lorenzi, PhD, stated: "It is entirely appropriate and timely to certify clinical informatics as a specialized area of training and expertise in an era when more and more clinicians are turning to data-driven, computer-assisted clinical decision support to provide care for their patients. Clinical informatics blends medical and informatics knowledge to support and optimize healthcare delivery."[1]

"The NLM [National Library of Medicine] has been funding education programs on medical informatics for over 40 years," says Page, whose program at the University of Wisconsin at Madison has been supported by NLM for 12 years. In fact, it is such a growing trend that it is estimated that 50,000 new medical informatics specialists are needed to meet the growing demand.[7] "Our students come from a variety of majors," adds Page, "from computer science, biochemistry, MDs, nurses and statisticians. It's a very large field and goes well beyond data analysis."

The Future of "Big Data"

"I'm trying to think about what this field will look like in five to 10 years," says Page. "I'm excited by the predictive models and what they mean for personalized medicine. I'd like to be able to predict who is most at risk for a heart attack, diabetes or cancer so that we can take action early. But, there is also the problem of adverse drug events. Is a new drug causing some specific subset of the population an adverse reaction that we didn't see in clinical trials because we were only looking at 1,000 people? Can we predict who is most likely to have an adverse event, and can we also identify for whom this drug is going to perform? If we can, we can incorporate these findings into EHRs so they can build predictive support. Then, we can build in pop-up alerts that this patient is at an increased risk for a heart attack, etc. For the most part, we are not at that point yet. [But,] as we collect more thorough genomic sequencing, data will greatly improve our ability to produce better medicine. I think that cancer research is where we'll see the biggest impact both short and long term. By genotyping a tumor, we can see the result of the disease, and companies are already looking at this."

"We are proud of this work," adds Ricciardi. "It requires future thought as to where we are going and how best to integrate all this care in a way that uses the right provider at the right time to improve the healthcare delivery system. Science administration is not easy, and it is important to invest our public's money wisely and engage the right people to provide the right guidance."

With an emphasis on "big data," medical informatics is changing the way we are thinking about making decisions. Says Page: "With personalized medicine and predictive analytics, we can do a better job of improving outcomes for patients." ❖

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References

1. Agency for Healthcare Research and Quality. 2012 *National Healthcare Quality Report*. Accessed at www.ahrq.gov/research/findings/nhqrdr/nhqr12/highlights.html.
2. American Medical Informatics Association. *Health Policy Meeting Briefing Book*. Accessed at www.amia.org/sites/amia.org/files/Invitational-2012-Health-Policy-Meeting-Briefing-Book.pdf.
3. U.S. Department of Health and Human Services Agency for Healthcare Research and Quality. USHIK 101 — A Quick Course in Metadata and Metadata Registries. Accessed at ushik.ahrq.gov/new_user.jsp?faq=q1&enableAsynchronousLoading=true.
4. Centers for Medicare and Medicaid Services. AHRQ Common Formats — Information for Hospitals and State Survey Agencies (SAs) - Comprehensive Patient Safety Reporting Using AHRQ Common Formats, March 15, 2013. Accessed at www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Policy-and-Memos-to-States-and-Regions-Items/Survey-and-Cert-Letter-13-19.html.
5. Health Data Management. Leveraging Advanced Analytics to Successfully Reduce Hospital Readmissions. Accessed at himss.files.cms-plus.com/FileDownloads/106420_0213.pdf.
6. Dolan, PL. Patients Seek Strong Say in How Their Data Are Used. *American Medical News*, Oct. 3, 2012. Accessed at www.amednews.com/article/20121003/business/310039997/8.
7. Dolan, PL. Clinical Informatics Now a Subspecialty. *American Medical News*, Oct. 10, 2011. Accessed at www.amednews.com/article/20111010/business/310109962/6.

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Increasing the Role of Pharmacists in Patient Care

By Amy Scanlin, MS

Allowing pharmacists to become more involved in patient care will reap benefits for patients and save healthcare dollars.

In the 1970s, a movement was started to allow pharmacists to provide more comprehensive care. Today, many feel the urgency for this to happen has never been greater. With 22 percent fewer general medicine physician graduates in the past 10 years, more medical graduates choosing fields other than primary care, and the addition of tens of millions of Americans who will be required to purchase health insurance in 2014 and beyond under the Affordable Care Act, it is predicted that there will be a dearth of providers to meet the needs of a growing number of insured and aging. But, by expanding pharmacists' role to be more than drug dispensers, many hope this strain on the healthcare system can be alleviated.

The Need for an Expanded Role

"The days when pharmacists were responsible for merely the physical act of prescriptions has gone the way of rotary dial phones. There is now an expectation that pharmacists have a duty to not only fulfill prescriptions, but to contribute to the overall clinical picture of our patients," says Amy Ehlers, BS, PharmD, BCPS, director of pharmacy at NuFACTOR Specialty Pharmacy. "Chronic disease care utilizes a large portion of healthcare's financial and professional resources. Physicians are seeing more patients with less time, and with the increasing amount of information available on the Internet, patients have more expectations and questions. Pharmacists are filling those gaps that are being created. There is a movement in pharmacy toward medication therapy management, which gives pharmacists opportunities to have a comprehensive review of patients' health and disease states and to address drug, nondrug and lifestyle changes that will give them the best chances of success in managing their diseases."

Ehlers' assessment is shared by many in the healthcare system. "I say it's the 50-year debate that ended just in time!" adds Lucinda Maine, CEO of the American Association of Colleges of Pharmacy (AACP). "Thoughtful people both inside and outside of pharmacy have realized that, as our society ages and we have more chronic disease and more need for medications, we need a new proactive medication management model."

According to Brian Meyer, director, government affairs at the American Society of Health-System Pharmacists (ASHP), the movement to change the medication management model "began in the late 1990s, when pharmacists were not being chosen to manage outpatient clinics that primarily involved medication therapy as the treatment plan in collaboration with prescribers because the clinics couldn't bill for their services." This is unlike other professions, explains Meyer. "For example, anticoagulation clinics were being managed by nurse practitioners since they were recognized by CMS [Centers for Medicare & Medicaid Services] as a provider."

Pharmacists' inability to be compensated because they are not yet recognized as a provider by Medicare Part D in the Social Security Act is one of the challenges to expanding the role of these specialists. "One of the impetuses for this push of pharmacists as providers is that hundreds of thousands of pharmacists don't get paid [for services]. Their pharmacy gets paid, but they don't," says Donnie Calhoun, National Community Pharmacists Association (NCPA) president and owner of Golden Springs Pharmacy in Anniston, Ala. "If I have a national provider identification number and someone can identify that I am the one who provided the services, why does my pharmacy get paid but I don't? Right now, we are only paid for dispensing."

"Recognizing pharmacists as providers under the Social Security Act would be a huge acknowledgment of the services pharmacists currently provide and allow that role to expand even further," says Ehlers. Right now, because "the Social Security Act does not recognize pharmacists as healthcare providers, services such as medication therapy management and consultations may not be billed to Medicare. Healthcare professionals such as dieticians, nurse practitioners, physician assistants, nurse midwives and clinical social workers are [recognized], so why not pharmacists?"

There is now an expectation that pharmacists have a duty to not only fulfill prescriptions, but to contribute to the overall clinical picture of our patients.

In fact, adds Ehlers, "pharmacists have long been the most accessible healthcare professionals and may be the first and last interaction that patients have in the healthcare system. Often, patients speak with their pharmacists regarding a health concern, and if pharmacists are unable to provide a solution, [they] will refer those patients to a provider for further evaluation. If prescriptions are provided, patients will return to those pharmacists. By including pharmacists in the Social Security Act, this will only drive further development of other opportunities in which pharmacists can have a positive impact. We're not looking to replace the unique services of providers such as physicians, physician assistants or nurse practitioners, but merely to enhance and augment them."

What Is and Needs to Be Done

Currently, pharmacists work in collaboration in varying degrees with physicians in 46 states.[1] For instance, some states have a collaborative effort to administer vaccines such as the flu vaccine, while others don't allow administration. "There are a few states, notably California and Kentucky, that are seeking revisions in state law. However, recognition in the Social Security Act can stimulate other payers, both public (states) and private, to follow suit," says Meyer.

The Congressional Budget Office says formalized patient-pharmacist counseling has been shown to produce as much as a 12-to-1 return on investment,[2] and the U.S. Surgeon General,

Regina Benjamin, has published a letter in support of the report titled *Improving Patient and Health System Outcomes through Advanced Pharmacy Practice — A Report to the U.S. Surgeon General, 2011*. That report is one of "a number of studies that outline the value of pharmacist-provided patient care services. These include medication reconciliation and transitional care services for patients being discharged from the hospital, helping patients adhere to their medication regimens and, in general, managing patients' medications for treatment of chronic disease," says Joseph M. Hill, director, federal legislative affairs at the ASHP.

Much more work needs to be done for this effort of inclusion of pharmacists as providers to come to fruition.

However, there is only so much money to be had, and adding pharmacists into the mix of providers is being met with some resistance. According to Maine of the AACP, the "demand for pharmacy services while working in close collaboration with other providers [can be met] … if we can secure regulatory authority and the payments to make this work — both big hurdles."

Much more work needs to be done for this effort of inclusion of pharmacists as providers to come to fruition. One bill that is being looked at is the Medication Therapy Management Benefits Act of 2011 that would offer patients better access to medication reviews and face-to-face counseling with licensed pharmacists. In addition, there is a nationwide movement to have the Social Security Act changed for this inclusion, which is seeing much support from many sides. Arguments by proponents that pharmacy services are already included in the essential health benefits package, as well as other parts of the new healthcare reform law, and that patients' overall quality of care will improve seem to be making traction. "This has become a major platform issue for a lot of major pharmacy groups," says Calhoun. "We are seeing a lot of state pharmacy associations giving legs to these grass-roots issues. By working together, we can make it a reality. We believe in this healthcare change. It's the right thing to do."

The ASHP argues that pharmacists who provide a more comprehensive and coordinated effort in patients' care must successfully demonstrate competencies through practice-intensive continuing education, pharmacy practice and specialty residencies. They also say that the role of pharmacists should be well defined within a scope-of-practice document or a similar tool developed by a healthcare organization.[3] "We view the evolution of pharmacist-provided patient care as one which is done in coordination with other healthcare providers. As care delivery moves toward team-based approaches, we don't view pharmacist patient care services as those done in a vacuum, but rather as part of a coordinated effort among all caregivers who are communicating with each other to provide the best, most cost-effective care possible," says Hill.

Since 2004, the standard accreditation for students in pharmacy school is a doctor of pharmacy, or PharmD, although those who graduated prior to that year were able to matriculate with a bachelor's degree. Currently, there are about an equal number of licensed pharmacists with either a bachelor's degree or a PharmD practicing, with about 60 percent of those employed by pharmacy chain stores. The AACP is currently revising its educational standards guideline, as it does every 10 years, and Maine says in addition to a rock solid foundation of anatomy, chemistry and biology, the core curriculum expectations that were simplified and set in 2004 (to provide pharmaceutical care, develop and manage systems of medication use to enhance public safety, and contribute to public health) will likely call for "soft skills" to be heightened such as making sure students can express compassion and have a cultural competency, as well as critical thinking and the ability to problem solve. "There are many tools in the toolbox," says Maine, where gaining educational and real world experience is concerned, including residencies, certifications and continuing education. In addition, adds Meyer of ASHP, "students are learning through their rotations and other course work that team-based, collaborative interdependent care with other health professionals will require them to function in new payment and delivery systems." Through its Pharmacy Practice Model Initiative, educational programming, and other initiatives, ASHP is providing opportunities for pharmacists to upgrade their skills and provide a range of services to patients.

Whether pharmacists have a bachelor's degree and more experience or are new PharmD graduates, Calhoun believes they have good experience and practice in communicating and understanding patients' needs, especially at the community pharmacy level where they may know their customers as neighbors. "I believe that pharmacists have the counseling skills because they already use them daily," he explains.

The Benefits of an Expanded Role

It is estimated that about 75 percent of the $2 trillion spent on healthcare is spent on the management of chronic diseases. The average adult fills about 12 prescriptions annually before

the age of 65. After 65, that number jumps to more than 30. And, it's not just adults; Medco Health Solutions found in an evaluation of prescription data that 30 percent of children age 19 and under take at least one chronic medication.[4]

Pharmacists can keep an eye on patients' use of medications and make sure they are taking them appropriately and, in some cases, remembering to take them at all. Studies show that only about half of patients take their meds as prescribed, and lack of adherence results in $290 million in medical costs annually.[1] "Communication and compliance are the keys to a successful and satisfied patient," explains Ehlers. "Patients who openly and willingly speak with their pharmacist about concerns or issues have the best chance to have the best outcomes. It is important for patients to know that there is not a 'one-size-fits-all' model for their care. For instance, if patients are having side effects, there are often alternatives or interventions that may be tried. But, if patients don't let their pharmacists know, pharmacists won't know to make changes. Also, patients need to be willing and able to follow the prescribed medication regimen. If patients are having difficulties with compliance for specific reason(s), that also needs to be discussed. Even the perfect medication regimen can't work if patients are unable or unwilling to follow it."

Pharmacists also can provide an educational component for patients who are unclear about why they are taking certain medications — a far cry from the 1950s and 1960s, when pharmacists had to refer patients back to their physician for any questions about their condition and the medications prescribed. "Pharmacists bring a strong set of needed skills to a patient's comprehensive care program," says Ehlers. "They are trained to be the drug experts and to have a thorough understanding of drugs and how they work — both within the body and with each other. By not taking advantage of this vast pool of information, providers are doing a disservice to both themselves and their patients."

Pharmacists trained at the doctoral level manage complex drug therapies, can interpret diagnostic laboratory results, and can refer patients to specialists, among many other duties. It is estimated that 92 percent of pharmacist recommendations in outpatient, inpatient and nursing home settings were approved by the patient's provider.[4]

"The VA has had a long history of including pharmacists in patient care," says Virginia Torrise, deputy chief consultant at the U.S. Department of Veterans Affairs Central Office. "In 1995, the Under Secretary of Veterans Affairs for Health authorized pharmacists to prescribe medications, and since then, pharmacists have had advanced roles in patient care and those roles continue to be expanded." The VA's comprehensive inclusion of pharmacists in patient care has allowed their role to change from disease-based to medication management-based care, where "providers refer patients to clinical pharmacists who help manage their clinical needs. There are as many as 40 different specialty care areas" [in which pharmacists have an integrated role in patient care].

"When we look at core practice areas, pharmacy specialists manage medications and more complex care such as blood products and transplant medications," says Julie Groppi, national director, Clinical Pharmacy Policy and Standards at the VA. Clinical pharmacists also review dosing and pharmaco parameters for patients. "Physicians are comfortable referring patients to pharmacists," adds Groppi. "They manage complex medications and help improve access to physicians. Patients appreciate the services the pharmacists provide, and they help reduce poly-pharmacy."

The VA is seeing the increased access to pharmacists as having a positive effect on their patient care and patient satisfaction. "A J.D. Power survey of both mail-order and brick-and-mortar pharmacies showed the VA had a high level of customer satisfaction, and pharmacists are at the heart of that," says Torrise.

From a financial standpoint, a Congressional Budget Office report released a new finding that changes in prescription drug use will bring about a change for medical services spending. Offsetting a 1 percent increase in the number of prescriptions filled will cause Medicare spending to fall by one-fifth of 1 percent, and thus have a positive impact on healthcare spending.[5] The VA reports similar results, with every $1 invested in clinical pharmacy services resulting in a $4 benefit, which can be extrapolated using average salary data to show a $368,000 savings benefit per provider of clinical pharmacy services.[6]

The VA is seeing the increased access to pharmacists as having a positive effect on their patient care and patient satisfaction.

According to Ehlers, studies have shown that the more pharmacists are involved in direct patient care, "medication 'misadventures' are decreased, outcomes are improved, and the overall cost of healthcare is reduced. According to a 2007 article in the *Journal of General Internal Medicine*, there were $3.5 billion in hospital costs saved by pharmacists coordinating medications from multiple prescribers."

Calhoun believes that if the Social Security Act is changed for the inclusion of pharmacists as providers, it will bring the cost of healthcare down: "If passed, an easy place for this to

start is with immunizations. We've already been doing it for years and years, but now pharmacists would get paid. Next, we'd look at other places where we could provide overall help, such as when a diabetic patient is discharged from the hospital. They would see a diabetes educator, who could then turn them over to a pharmacist who can monitor them and follow up with the patient's physician. We can grow that market basket of services pharmacists can perform. We won't have to be constrained by those four walls. A pharmacist who is a diabetic expert could have appointments set up at 10 different clinics, and that is how we are going to keep costs down — with more collaborative care."

The number of pharmacists certified to administer vaccinations has quadrupled since 2007, according to the American Pharmacists Association. It is estimated that 18.4 percent of patients who received a flu shot in the 2010-2011 season did so by their pharmacist.[7] Other areas where pharmacists are making an impact include providing health promotion and disease prevention guidance, and performing some limited physical assessments and supervising medication therapy with appropriate collaborative drug therapy management (CDTM) authority. CDTM allows pharmacists to enter into an agreement with a physician for the care of patients who have a confirmed diagnosis, enabling them to work with patients in defining an appropriate medication therapy and adjust that therapy as needed.[3]

However, not everyone is entirely happy about the push to increase a pharmacist's role in patient care, particularly with regard to writing prescriptions. The American Association of Family Physicians (AAFP), for one, supports pharmacists as an "integral part of an integrated team-based approach to care"; however, the association urges caution. "Only licensed doctors of medicine, osteopathy, dentistry and podiatry should have the statutory authority to prescribe drugs for human consumption"[8] it argues, because allowing pharmacists to prescribe drugs will further fragment the already fragile healthcare system and limit integrated and accountable care.

While medication management programs are a positive for patient healthcare, and those programs oftentimes are run by pharmacists, it is the association's belief that pharmacists should not prescribe medications. "This is an important issue as we move forward with new models of patient care," says Jeff Cain, MD, president of AAFP. "If everyone on the team collaborates, we will have better coordinated care, and that means better quality of care for patients, as well as reduced costs." However, Cain fears, if healthcare is "fragmented" or there are more individual players, patient care will be hampered by many instances of duplication of care. "If we fragment care, it adds to the complexity," he adds. "We will see increased testing, increased orders for X-rays, increased orders for labs and increased errors, and that will increase the frustration levels of patients, and they will have more unmet medical needs. We won't be recognizing the whole person. This will lead to more unnecessary rehospitalizations and ER visits."

A Collaborative Effort

Cain says that by working collaboratively, there will be enough providers to cover the influx of new patients under the Affordable Care Act: "These are all high-quality members [of the medical team] working together to reach common goals. There are some very good examples of high collaboration with very good primary care, which increases the functionality of each team member."

"It's dicey," says Maine of the challenges that lie ahead. "We've got to have a dialogue with organized medicine. Medicare Part D, billing authority — it's a bowl that [financially] is not getting any bigger." However, as the flood of people pour in with the Affordable Care Act, "it's going to be all hands on deck! We sense a stronger commitment by more organizations than in the past, and we must work together with cohesiveness and commitment. There really is no time frame [for moving forward legislatively]; however, those who are the most aggressive in their thinking would like to see something in terms of an 'ask' not an 'outcome' by the end of 2013." ❖

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References

1. Andrews M. Pharmacists Expand Role to Help Educate and Coach Patients. *Kaiser Health News*, March 15, 2011. Accessed at www.kaiserhealthnews.org/features/insuring-your-health/michelle-andrews-on-pharmacy-outreach-and-chronic-health-problems.aspx.
2. Hoey BD. Community Pharmacists Can Help Improve Health Outcomes, Reduce Costs. The Hill.com. Accessed at www.ncpanet.org/index.php/ncpa-commentary/999-community-pharmacists-can-help-improve-health-outcomes-reduce-costs.
3. American Society of Healthsystem Pharmacists Statement on the Pharmacist's Role. Accessed at www.ashp.org/DocLibrary/BestPractices/SpecificStPrimary.aspx.
4. Manolakis PG, Skelton JB. Pharmacists' Contributions to Primary Care in the U.S. — Collaborating to Address Unmet Patient Care Needs. The American Association of Colleges of Pharmacy, July 2009. Accessed at www.hrsa.gov/publichealth/clinical/patientsafety/aacp-brief.pdf.
5. Hayford T, Buntin M. CBO Estimates that Greater Prescription Drug Use by Medicare Beneficiaries Reduces Medicare's Spending for Medical Services. Congressional Budget Office, Nov. 29, 2012. Accessed at www.cbo.gov/publication/43742.
6. Patel RJ, et al. Pharmacists' Contributions to Primary Care in the United States Collaborating to Address Unmet Patient Care Needs: The Emerging Role for Pharmacists to Address the Shortage of Primary Care Providers. *Am J Managed Care*. 1999; 5:465-74.
7. Roth JR, Hoey BD. Don't Overlook a Local Health Resource: Pharmacists. National Community Pharmacists Association. Accessed at www.ncpanet.org/index.php/ncpa-commentary/1510-dont-overlook-a-local-health-resource-pharmacists.
8. American Academy of Family Physicians. AAFP Defines Role of Pharmacists, Family Physicians in Health Care Delivery System, Jan. 18, 2012. Accessed at www.aafp.org/online/en/home/publications/news/news-now/inside-aafp/20120118pharmacypaper.html.

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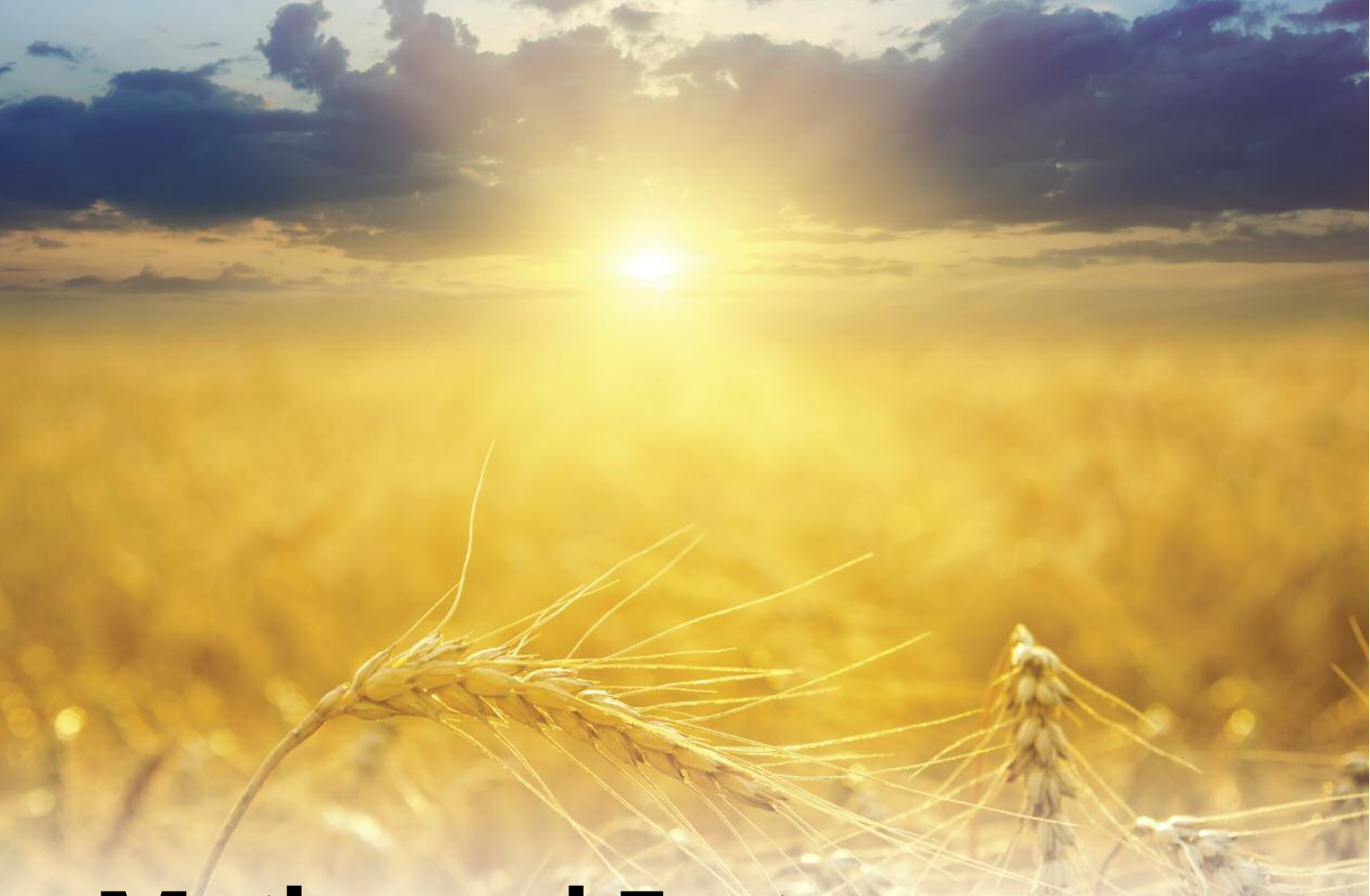

Myths and Facts: Celiac Disease

By Ronale Tucker Rhodes, MS

Because of a misunderstanding by physicians about the symptoms of celiac disease and how to diagnose it, many believe that only a fraction of individuals with the disease have been diagnosed.

More than one in 200 healthy individuals in the U.S. are diagnosed with celiac disease. The autoimmune disorder is triggered by dietary gluten that damages the villi (tiny finger-like projections that absorb nutrients from food) in the small intestine, leaving a smooth lining that can no longer absorb nutrients.[1,2]

"Celiac" comes from the Greek word for "abdominal."[2] Arataeus of Cappadocia was the first person to discover celiac disease in the second century, when he recorded a malabsorptive syndrome with chronic diarrhea, which he termed "coeliac affection." His work gained attention when it was presented at the Sydenham Society in 1856 in which Arataeus described his

"atrophied, pale, feeble and incapable-of-work" patient as having "stomach pain and diarrhea that manifested as loose stools that were white, malodorous and flatulent." He believed it was an affliction of the old that more commonly affected women (and never affected children) due to a lack of heat in the stomach necessary to digest food and a reduced ability to distribute digestive products throughout the body.[3]

The link between wheat products and celiac disease wasn't made until the 1940s by Dutch pediatrician Willem Dicke during the Dutch famine in 1944, when flour was sparse. Then, in 1954, the link between the gluten component of wheat was made, when British physician John W. Paulley was able to examine biopsies taken from patients during abdominal operations.[3]

Today, it is believed that many people have undiagnosed celiac disease as a result of misunderstandings on the part of physicians.[1] And, because this disease can cause serious complications if left undiagnosed, it is critical that the facts are separated from the myths about celiac disease so patients can be correctly and swiftly diagnosed and properly treated.

Separating Myth from Fact

Myth: Celiac disease is merely a gastrointestinal (GI) disease that causes chronic diarrhea.

Fact: Celiac disease is not a GI disease. While classic symptoms include abdominal pain, abdominal distension, diarrhea and constipation, many patients with celiac disease lack any GI complications. Instead, they may experience many extraintestinal presentations, including dermatitis herpetiformis, permanent enamel hypoplasia, iron deficiency anemia that is resistant to oral iron therapy, short stature and/or delayed puberty, chronic hepatitis and hypertransaminasemia, primary biliary cirrhosis, arthritis, osteopenia/osteoporosis, epilepsy with occipital calcifications, primary ataxia, psychiatric disorders and infertility.[1]

Myth: Celiac disease is a childhood disease.

Fact: The condition affects both children and adults. In young children, celiac disease most commonly is detected typically months after cereals have been introduced to the diet. In older children and adults, the disease is frequently diagnosed following various challenges to the immune system such as infections, pregnancy and childbirth, and surgery.[1]

Myth: Celiac disease is genetic and, therefore, it can't be prevented.

Fact: Celiac disease is an immune-mediated disease of the intestines that is triggered by the ingestion of gluten (the major protein component of wheat, rye and barley) in genetically susceptible individuals. Considerable progress has been made in identifying genes that play a role in celiac disease. It is now well known that celiac disease is strongly associated with specific HLA class II genes known as HLA-DQ2 and HLA-DQ8 located on chromosome 6p21.

Approximately 95 percent of celiac disease patients express HLA-DQ2, and the remaining patients are usually HLA-DQ8 positive. However, the HLA-DQ2 gene is common and is carried by approximately 30 percent of Caucasian individuals. Therefore, HLA-DQ2 or HLA-DQ8 is necessary for disease development, but not all people who have one of those genes will develop the disease; their estimated risk effect is only 36 percent to 53 percent.[4]

Some researchers believe that celiac disease may be triggered by the combination of having the gene(s) that make one susceptible, exposure to gluten and exposure to a toxin or an infection (such as a rotavirus). HLA tests for the HLA-DQ2 and HLA-DQ8 genes are commercially available from the following companies: Kimball Genetics (www.kimballgenetics.com), LabCorp (www.labcorp.com), Quest Diagnostics (www.questdiagnostics.com) and Specialty Laboratories (www.specialtylabs.com).[4]

An estimated 1 percent of the U.S. population (three million Americans) has celiac disease.

Whether the disease can be prevented is an area of ongoing research. There is some evidence that introducing gluten while breastfeeding (and not before 4 months of age) may be helpful, and a rotavirus vaccine may help to prevent an infection that might trigger the disease. Because celiac disease has a genetic link, it is recommended that parents and siblings of individuals diagnosed with celiac disease be tested, regardless of whether they are showing any symptoms.[2]

Myth: Celiac disease is rare.

Fact: An estimated 1 percent of the U.S. population (three million Americans) has celiac disease. Yet, because 20 percent to 30 percent of the world's population has been found to carry the HLA-DQ2 or HLA-DQ8 gene associated with a genetic susceptibility to celiac disease, it is believed that 95 percent of celiacs still go undiagnosed.[5]

Myth: Celiac disease has obvious symptoms.

Fact: Symptoms of the disease vary from person to person. Some exhibit no symptoms at all, while others suffer chronic symptoms. In children under 3 years old, the classic symptoms include abdominal pain and/or cramps, abdominal distension

(bloating), diarrhea, constipation, nausea, vomiting, decreased appetite, increased fatigue, weight loss or poor weight gain, short stature or poor growth, and frequent mouth ulcers. Older children and adults often experience different symptoms, including delayed puberty, behavioral problems, iron deficiency, osteopenia/osteoporosis, hepatitis, arthritis, infertility, migraines, seizures and neuropathy.[2]

Myth: Physicians are very aware of the symptoms of celiac disease and how to diagnose it.

Fact: In a survey conducted in 2005, researchers sought to determine physician awareness of celiac disease. Surveys completed by 2,440 (47 percent) of 5,191 patients in a support group were analyzed for frequency of diagnosis by physician specialties. In addition, questionnaires sent to 132 primary care physicians in a Southern California county were assessed to determine their knowledge of celiac disease. In patient surveys, only 11 percent were diagnosed by primary care physicians (PCPs — internists and family physicians) versus 65 percent by gastroenterologists. Physician surveys (70 percent response) showed that only 35 percent of PCPs had ever diagnosed celiac disease. Almost all physicians (95 percent) knew of wheat intolerance, but few (32 percent) knew that onset of symptoms of celiac disease in adulthood is common. Physicians were well aware (90 percent) of diarrhea as a symptom, but fewer knew of common symptoms of irritable bowel syndrome (71 percent), chronic abdominal pain (67 percent), fatigue (54 percent), depression and irritability (24 percent) or of associations with diabetes (13 percent), anemia (45 percent) or osteoporosis (45 percent), or of diagnosis by endomysial antibody tests (44 percent). The researchers' conclusion: Lack of physician awareness of adult onset symptoms, associated disorders and use of serology testing may contribute to the underdiagnosis of celiac disease.[7]

Whether the disease can be prevented is an area of ongoing research.

Myth: Celiac disease can be diagnosed with a blood test.

Fact: The diagnosis of celiac disease starts with blood screening, including antiendomysial antibody (EMA) or antitissue transglutaminase (tTG) and the determination of total serum IgA level. The EMA and tTG tests are two different methods to measure the presence of the same antibody. However, if the total serum IgA level is normal, these tests have a very high negative predictive value for patients ages 2 through 50. Therefore, a positive test result must be made through an intestinal biopsy, the only definitive means of diagnosing celiac disease. The gold standard for diagnosing the disease is an esophagogastroduodenoscopy (EGD) with multiple biopsies of the duodenum and jejunum. In the early 1990s, a select panel of experts from the European Society for Pediatric Gastroenterology and Nutrition formulated diagnostic guidelines for celiac disease that are currently accepted worldwide. These guidelines stipulate that obtaining an intestinal biopsy is mandatory for the final diagnosis of the disease.[1,6]

Myth: Undiagnosed celiac disease is not serious.

Fact: There are many complications that can occur when celiac disease goes undiagnosed. In both children and adults, celiac disease can result in malnutrition. The damage to the small intestine means it can't absorb enough nutrients, which can lead to anemia and weight loss, and in children, it may cause stunted growth and delayed development. Malabsorption of calcium and vitamin D also can lead to softening of the bone (osteomalacia, or rickets) in children, a loss of bone density (osteoporosis) in adults, and can contribute to reproductive issues such as infertility and miscarriage. Small intestine damage also may cause people to experience abdominal pain and diarrhea after eating lactose-containing dairy products. And, people with celiac disease who don't maintain a gluten-free diet have a greater risk of developing several forms of cancer, including intestinal lymphoma and small bowel cancer.

As many as 15 percent of people have nonresponsive celiac disease often due to contamination of the diet with gluten. And these individuals often have additional conditions such as bacteria in the small intestine, colitis, poor pancreas function or irritable bowel syndrome. In rare instances, the injury to the intestine continues even though a gluten-free diet is adhered to.[8]

Individuals with celiac disease also develop genetic and autoimmune conditions. Common genetic disorders consist of Down syndrome, Turner syndrome and Williams syndrome. Common autoimmune diseases include type 1 diabetes, hyperthyroidism, hypothyroidism, Sjogren's syndrome and other connective-tissue diseases, and primary biliary cirrhosis.[1,2]

A study conducted at the University of Trieste in Italy found that the prevalence of autoimmune disorders in those with celiac disease is related to the duration of exposure to gluten. Over a six-month period, 909 patients with celiac disease grouped according to age at diagnosis (group one: less than 2 years; group two: 2 years to 10 years; and group three: older than 10 years), 1,268 healthy controls and 163 patients with Crohn's disease were evaluated for the presence of autoimmune disorders. The prevalence of autoimmune disorders among celiac disease patients was significantly higher than in healthy controls, but it was not higher than in Crohn's disease patients. However, in celiac disease patients older than 10 years

of age, the prevalence of autoimmune disorders was significantly higher than in those with Crohn's disease. Therefore, it was determined that age at diagnosis (hence, exposure to gluten) was the only significant predictor variable of the odds of developing an autoimmune disorder.[9]

Myth: There are many different types of treatment for celiac disease.

Fact: A strict, zero-tolerance gluten-free diet is the only treatment for celiac disease, and it is a lifelong treatment.[1] Even celiac disease patients who may seem to tolerate gluten are still causing damage to the intestinal lining when only a small amount of dietary gluten is consumed once in a while.[6]

Myth: A gluten-free diet means that only wheat and wheat byproducts need to be avoided.

Fact: Celiacs must avoid all wheat products, including kamut, semolina, durum, spelt, faro and einkorn. But, they must also avoid rye, barley and oats.[5]

Myth: It's not easy to find information about how to prepare meals on a gluten-free diet.

Fact: A number of websites are dedicated to educating diners and providing menu information for gluten-free options. For instance, glutenfreemenus.net lists chain restaurants such as PF Chang's and Bonefish Grill that offer gluten-free options on their menus. And, glutenfreerestaurants.com lists restaurants participating in the Gluten-Free Restaurant Awareness Program. There also is a magazine titled *Gluten-Free Living* that offers recipes, substitutions, advice from doctors and other helpful tools for living with celiac disease.[5]

Myth: Those with celiac disease can't consume beer.

Fact: While celiacs have always been able to drink wine and hard alcohol, until recently, most beers were off limits. Now, however, many companies have started producing gluten-free brews made from rice, buckwheat, corn and other safe-to-consume grains. The most common varieties today are Redbridge Beer produced by Anheuser-Busch and Bard's Tale Beer, which is made from sorghum and widely found at Whole Foods. Celiac patients are urged to be cautious, though, of international gluten-free beers because standards vary by country, and many of these beers may still contain remnants of the protein.[5]

Myth: Once diagnosed with celiac disease, an individual does not need further medical or dietary supervision.

Fact: Celiac disease is diagnosed after damage has occurred to the intestine. As a result, celiacs need continued medical and dietary supervision to prevent and treat anemia, osteoporosis and other nutritional deficiencies. Supervision also is important for early recognition and therapy of associated diseases such as diabetes and thyroid disease. And, to ensure a strict gluten-free diet, it's recommended that patients follow up with a dietitian to keep up to date with gluten-free dietary changes and to consult with pharmacists to help identify which drugs may contain gluten.[5]

Dispelling the Myths Now

It is believed that only a fraction of the suspected number of individuals who have celiac disease have been diagnosed. However, once diagnosed, celiacs must adhere to a lifelong gluten-free diet that often can be confusing and, in some cases, costly. Nutritional labels have improved, but the law requires only eight of the most common allergens to be listed on food labels (this includes wheat, but not barley or rye). And, the term "gluten-free" is generally used to indicate a supposedly harmless level of gluten, rather than a complete absence. For standardization, the U.S. Food and Drug Administration is considering a legal definition for gluten-free. In the next year or two, it's possible that gluten-free will mean an infinitesimal amount of gluten, perhaps along the lines of 20 parts per million. What's more, there is a significant lobby to make gluten-free foods covered by health insurance.[2]

There are many complications that can occur when celiac disease goes undiagnosed.

As awareness continues to grow about celiac disease, it is hoped that more people will be correctly diagnosed, the number of other complications stemming from this disease will decrease, and a gluten-free diet will be easier to follow. ❖

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References

1. Guandalini, S, and Melin-Rogovin, M. Celiac Disease: Myths and Facts. Gastroenterology. University of Chicago Medical Center. Accessed at theglutensyndrome.net/Celiac_Myths_FactsGuandalini_002799.pdf.
2. Boston Children's Hospital. Celiac Disease. Accessed at www.childrenshospital.org/az/Site669/mainpageS669P1.html.
3. Who first discovered celiac disease, and when was it first discovered? Askville by Amazon. Accessed at askville.amazon.com/discovered-Celiac-Disease/AnswerViewer.do?requestId=10919424.
4. Genetics of Celiac Disease. Medscape Reference. Accessed at emedicine.medscape.com/article/1790189-overview.
5. Gil, V. 10 Myths and Facts about Celiac Disease. Food Republic. Accessed at www.foodrepublic.com/2011/05/18/10-myths-and-facts-about-celiac-disease.
6. Canadian Celiac Association. Celiac Disease Myths & Facts. Accessed at calgaryceliac.com/CCA/wp-content/uploads/2012/03/celiac-disease-myths-facts.pdf.
7. Zipser, RD, Farid, M, Baisch, D, Patel, B, and Patel, D. Brief Report: Physician Awareness of Celiac Disease. *Journal of General Internal Medicine*, 2005 July; 20(7): 644-646. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC1490146.
8. Mayo Clinic. Celiac Disease Complications. Accessed at www.mayoclinic.com/health/celiac-disease/DS00319/DSECTION=complications.
9. Ventura, A, Magazzu, G, and Greco, L. Duration of Exposure to Gluten and Risk for Autoimmune Disorders in Patients with Celiac Disease. *Gastroenterology*, 1999 Aug; 117(2): 297-303.

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*US deaths from flu have ranged from 3000 to about 49,000 per year.[1]
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In 2009, 28,000 men died from prostate cancer[2] and more than 40,000 women from breast cancer.[3] And while influenza may not seem like a serious disease, each year it causes 3000 to 49,000 flu-associated deaths.[1]

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

Novartis Vaccines is committed to providing seasonal flu vaccine doses on time. In fact, in 2012, Novartis Vaccines completed the shipping of more than 36 million seasonal flu vaccine doses ahead of schedule, allowing for early and convenient administration.

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

Indication

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

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

Important Safety Information

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

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

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

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

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

Vaccination with FLUVIRIN® may not protect all individuals. In clinical trials, the most common adverse events in adults were headache, fatigue, injection site reaction (pain, mass, redness, and induration), and malaise.

Please see brief summary of the Fluvirin Prescribing Information on the following pages.

References: 1. Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza—United States, 1976–2007. *MMWR Morb Mortal Wky Rep*. 2010;59(33):1057-1062. **2.** Centers for Disease Control and Prevention. Prostate Cancer Statistics. www.cdc.gov/cancer/prostate/statistics. Accessed May 8, 2013. **3.** Centers for Disease Control and Prevention. Breast Cancer Statistics. www.cdc.gov/cancer/breast/statistics. Accessed May 8, 2013. **4.** Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep*. 2010;59(RR-8):1-62.

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NOVARTIS
VACCINES AND DIAGNOSTICS

Influenza Virus Vaccine
Fluvirin®

FLUVIRIN® (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
2012-2013 Formula
Initial US Approval: 1988

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

1 INDICATIONS AND USAGE

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

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

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer FLUVIRIN® to anyone with known history of severe allergic reactions (e.g., anaphylaxis) to egg proteins (eggs or egg products), or to any component of FLUVIRIN®, or who has had a life-threatening reaction to previous influenza vaccinations.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

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

5.2 Altered Immunocompetence

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

5.3 Preventing and Managing Allergic Reactions

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

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

5.4 Limitations of Vaccine Effectiveness

Vaccination with FLUVIRIN® may not protect all individuals.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

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

6.2 Clinical Trial Experience

Adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating the rates of these events. However, because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect rates observed in clinical practice.

Adult and Geriatric Subjects

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

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

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

TABLE 2
Solicited Adverse Events in the First 72-96 Hours After Administration of FLUVIRIN® in Adult (18-64 years of age) and Geriatric (≥65 years of age) Subjects.

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

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

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

TABLE 3
Solicited Adverse Events in the First 72 Hours After Administration of FLUVIRIN® in Adult Subjects (18-49 years of age).

	2005-2006 US Trial FLUVIRIN® N = 304
Local Adverse Events	
Pain	168 (55%)
Erythema	48 (16%)
Ecchymosis	22 (7%)
Induration	19 (6%)
Swelling	16 (5%)
Systemic Adverse Events	
Headache	91 (30%)
Myalgia	64 (21%)
Malaise	58 (19%)
Fatigue	56 (18%)
Sore throat	23 (8%)
Chills	22 (7%)
Nausea	21 (7%)
Arthralgia	20 (7%)
Sweating	17 (6%)
Cough	18 (6%)
Wheezing	4 (1%)
Chest tightness	4 (1%)
Other difficulties breathing	3 (1%)
Facial edema	-

Results reported to the nearest whole percent
– not reported

TABLE 4
Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998

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

	2001-2002^		2002-2003^		2004-2005^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Adverse Events						
Fatigue	5 (7%)	4 (11%)	11 (10%)	8 (9%)	4 (5%)	2 (3%)
Hypertension	-	-	1 (1%)	4 (5%)	-	-
Rinorrhea	-	-	2 (2%)	5 (6%)	-	-
Headache	20 (27%)	2 (6%)	35 (33%)	18 (20%)	12 (16%)	1 (2%)
Malaise	6 (8%)	1 (3%)	13 (12%)	8 (9%)	-	-
Myalgia	4 (5%)	1 (3%)	10 (9%)	4 (5%)	-	-
Sweating	3 (4%)	3 (9%)	2 (2%)	5 (6%)	-	-
Rhinitis	4 (5%)	-	-	-	-	-
Pharingitis	-	-	-	-	6 (8%)	-
Arthralgia	-	-	5 (5%)	4 (5%)	-	-
Sore throat	4 (5%)	1 (3%)	5 (5%)	4 (5%)	-	-
Injection site pain	13 (17%)	3 (9%)	14 (13%)	7 (8%)	6 (8%)	2 (3%)

(continued)

TABLE 4
Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998

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

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

Adults (18 to 64 years of age)
In adult subjects, solicited local adverse events occurred with similar frequency in all trials. The most common solicited adverse events occurring in the first 96 hours after administration (Tables 2 and 3) were associated with the injection site (such as pain, erythema, mass, induration and swelling) but were generally mild/moderate and transient. The most common solicited systemic adverse events were headache and myalgia.

The most common overall events in adult subjects (18-64 years of age) were headache, fatigue, injection site reactions (pain, mass, erythema, and induration) and malaise (Table 4).

Geriatric Subjects (65 years of age and older)
In geriatric subjects, solicited local and systemic adverse events occurred less frequently than in adult subjects. The most common solicited local and systemic adverse events were injection site pain, and headache (Tables 2 and 3). All were considered mild/moderate and were transient.

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

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

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

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

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

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

- *Body as a whole:* Local injection site reactions (including pain, pain limiting limb movement, redness, swelling, warmth, ecchymosis, induration), hot flashes/flushes; chills; fever; malaise; shivering; fatigue; asthenia; facial edema.
- *Immune system disorders:* Hypersensitivity reactions (including throat and/or mouth edema). In rare cases, hypersensitivity reactions have lead to anaphylactic shock and death.
- *Cardiovascular disorders:* Vasculitis (in rare cases with transient renal involvement), syncope shortly after vaccination.

- *Digestive disorders:* Diarrhea; nausea; vomiting; abdominal pain.
- *Blood and lymphatic disorders:* Local lymphadenopathy; transient thrombocytopenia.
- *Metabolic and nutritional disorders:* Loss of appetite.
- *Musculoskeletal:* Arthralgia; myalgia; myasthenia.
- *Nervous system disorders:* Headache; dizziness; neuralgia; paraesthesia; confusion; febrile convulsions; Guillain-Barré Syndrome; myelitis (including encephalomyelitis and transverse myelitis); neuropathy (including neuritis); paralysis (including Bell's Palsy).
- *Respiratory disorders:* Dyspnea; chest pain; cough; pharyngitis; rhinitis.
- *Skin and appendages:* Stevens-Johnson syndrome; sweating; pruritus; urticaria; rash (including non-specific, maculopapular, and vesiculobulbous).

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

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

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

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

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

16 STORAGE AND HANDLING

16.2 Storage and Handling
Store FLUVIRIN® refrigerated between 2° and 8°C (36° and 46°F).

Do not freeze. Discard if the vaccine has been frozen.

Store in the original package to protect from light.

Do not use after the expiration date.

Between uses, return the multidose vial to the recommended storage conditions.

FLUVIRIN® is a registered trademark of Novartis Vaccines and Diagnostics Limited.

Manufactured by: Novartis Vaccines and Diagnostics Limited, Speke, Liverpool, UK
An affiliate of: Novartis Vaccines and Diagnostics, Inc.,
350 Massachusetts Avenue, Cambridge, MA 02139 USA
1-877-683-4732

Man Versus Flu: The Search for a Universal Influenza Vaccine

Let me tell you the secret that has led me to my goal: My strength lies solely in my tenacity.

— Louis Pasteur

BY KEITH BERMAN, MPH, MBA

NO ONE CAN argue that there are not plenty of options these days for annual immunization against the flu. For the 2013-14 season, seven manufacturers — up from four a decade ago — are offering a smorgasbord of inactivated and live-attenuated and recombinant, trivalent and quadrivalent, standard and high-dose, and intramuscular and intranasal and intradermal flu vaccines.

Yet despite the panoply of choices, influenza remains a serious public health threat. The most recent 2012-13 flu season presents a sobering reminder of the limits of our current vaccine technology. While flu vaccines were 56 percent effective for all recipients, they were just 9 percent effective for persons age 65 and older. The number of flu-related pediatric deaths during last year's flu season was the highest reported since data collection began in 2004.[1] The hospitalizations avoided and lives saved by current-generation flu vaccines unquestionably justify the annual effort and cost of hunting down target strains, then manufacturing and administering around 135 million vaccine doses this season.[2] But this winter, tens of millions of Americans will come

down with the flu (including many, of course, who neglect to get their annual flu shot), millions of workdays will be lost, as many as 200,000 or more people may be hospitalized, and thousands will die from flu-related complications.

The obvious need remains for "a vaccine that you don't have to give every year that works better," said Dr. Joseph Bresee, a senior epidemiologist in Centers for Disease Control and Prevention's (CDC's) Influenza Division.[3] "Among the two dozen vaccine-preventable diseases, including measles, mumps, polio, smallpox and hepatitis, seasonal influenza is the only one for which a new vaccine is recommended every year. A more efficient approach is long overdue," noted Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases.[4]

Possibly the best evidence for the feasibility of a longer-acting, broadly protective "universal" flu vaccine comes from a natural experiment — the surprisingly mild 2009 H1NI flu pandemic. Antigenically distinct from recently circulating H1N1 seasonal flu viruses, that H1N1 virus turned out to be a distant relative of the virus responsible for the devastating 1918 Spanish flu pandemic. A new analysis by scientists at the Wistar Institute has revealed that people of different ages experienced vastly different antibody response rates to the 2009 H1N1 pandemic virus, depending on whether they were exposed to a seasonal H1N1 virus many decades earlier.[5] This new understanding that our immune systems can "remember" and generate neutralizing antibodies to similar-looking flu strains has bolstered enthusiasm about the prospects for a universal vaccine or vaccine cocktail.

Influenza Viruses as Escape Artists

Despite their different production processes, presentations and delivery options, all licensed influenza vaccines work by inducing protective humoral immunity against antigenic targets on the globular "head" portion of hemagglutinin (HA), a surface glycoprotein that the virus uses to attach itself to respiratory tract and other host cells (Figure 1). When exposed to the circulating live flu virus, the immunized individual rapidly produces specific antibodies that inhibit virus infection by blocking HA attachment to our cells. Yet, when the next flu season rolls around, without immunization against the new epidemic strain, we are once again susceptible to contracting the illness.

Influenza viruses exploit three potent evolutionary strategies that enable them to return to infect us again and again.

Influenza viruses exploit three potent evolutionary strategies that enable them to return to infect us again and again. The error-prone replication of viral RNA strands in the human or other mammalian host cell generates spontaneous mutations that translate into changes focused in particular in the polymorphic head portion of the viral HA surface protein. *Antigenic shift* occurs when significant mutations create new flu viruses that are poorly recognized by large segments of the population.

As a growing portion of the flu-infected — or vaccinated — population builds effective neutralizing antibodies against the prevalent influenza virus strains, natural selection favors new variants that are capable of escaping host immunity by virtue of their altered HA protein structure. Thus, we see *antigenic drift* of the flu viruses that circulate over the course of each season. The greater the mismatch between the drifted virus strains and the early virulent strains against which the season's flu vaccine was manufactured, the more the efficacy of the vaccine is diminished.

Periodic flu pandemics occur when entirely new influenza virus subtypes are created by genetic *reassortment* when two different viruses co-infect the host cell. Unlike most viruses that have a single RNA strand, the flu virus includes eight RNA strands to encode its genome. When all those strands intermix, a novel "reassortant" progeny virus can be created that never existed before. The H1N1 strain that caused the 2009 swine flu pandemic, for example, was a complex reassortant of avian,

Figure 1. Stucture of the Hemagglutinin (HA) Protein

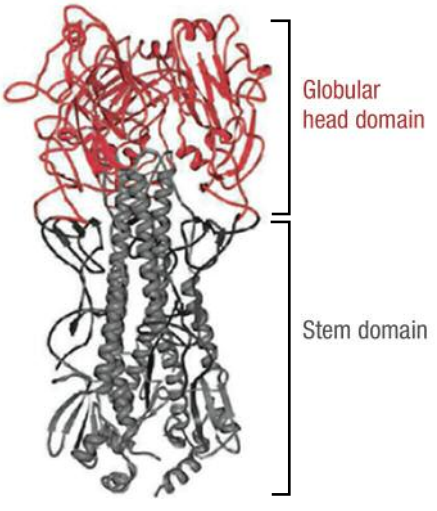
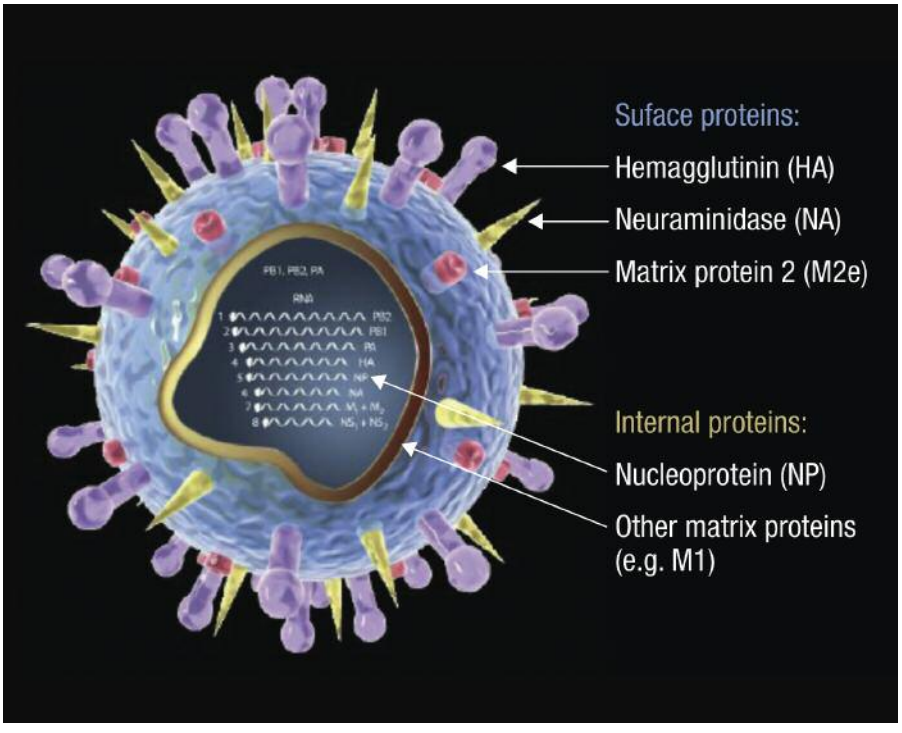


Figure 2. Influenza Virus: Potential Target Antigens for a Universal Vaccine



human and swine influenza viruses that further reassorted with a Eurasian swine flu virus.[6] But as a growing share of the population was exposed to it, immune selection resulted in antigenic drift of the 2009 H1N1 virus, resulting in its transition to a seasonal flu virus.

Thus, the flu virus rebounds to create new epidemics each year by continually changing its antigenic presentation, which both necessitates the annual licensure and production of new vaccines, and leaves us highly vulnerable to the next flu pandemic. But encouraging recent findings reported by some laboratories have raised hopes that a long-dreamed-about strategy of targeting highly conserved viral proteins could yield broadly protective "universal" vaccines that confer long-term protection against both drifted and pandemic influenza A and B.

Universal Flu Vaccine Candidates

The functional premise of most development-stage universal influenza A and B vaccines is simple: Induce highly cross-reactive antibodies against highly conserved antigenic targets across different influenza virus subtypes and strains (Figure 2). Most promising development-stage vaccines incorporate one or more of the following three viral proteins:

• *Hemagglutinin A (HA) stem region.* Also referred as the HA stalk, this region of the HA glycoprotein is highly conserved. One group has designed a novel vaccine that includes the stem portion of HA without the globular head; mice vaccinated with this "headless HA" were completely protected against a lethal influenza virus challenge.[7] Separately, researchers at the Scripps Research Institute report isolating a monoclonal antibody (MAb) that recognizes a highly conserved epitope on the stem region of HA and neutralized influenza virus by preventing virus-host membrane fusion.[8] They and others have subsequently identified other MAbs that target the HA stem region, creating an entirely separate theoretical opportunity to produce a MAb cocktail that could be used to provide passive immunity in cases of severe influenza.[9]

• *Matrix protein 2 (M2e).* This highly conserved external domain of this influenza A surface glycoprotein plays a key role in virus morphogenesis and assembly. On hopes that it can induce cross-protection against different subtypes, M2e has been selected for a number of universal influenza A vaccine candidates. To improve its immunogenicity, several groups have linked M2e to such platforms as hepatitis B virus core,

By the end of the last decade, cautious optimism was being expressed at research conferences that the first universal vaccine could be available in as little as five years.

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To find out where to get your FLUCELVAX shot, go to FLUCELVAX.com.

What is FLUCELVAX® (Influenza Virus Vaccine)?

FLUCELVAX (Influenza Virus Vaccine) is a vaccine that helps protect against influenza (flu).

FLUCELVAX is for people aged 18 and older. Vaccination with FLUCELVAX may not protect all people who receive the vaccine.

Important Safety Information for FLUCELVAX

Who should not get FLUCELVAX?

- You should not get FLUCELVAX if you have had a severe allergic reaction to any of the ingredients in the vaccine

Who may not be able to get FLUCELVAX?

Tell your healthcare provider if you:

- have ever had Guillain-Barré Syndrome (severe muscle weakness) after getting a flu shot
- have an allergy to rubber latex

What if I have a weakened immune system?

Tell your healthcare provider if you have problems with your immune system, as your immune response to the vaccine may be less.

Please see brief summary of Prescribing Information for FLUCELVAX on adjoining pages.

What are the most common side effects of FLUCELVAX (Influenza Virus Vaccine)?

- pain or redness where you got the shot
- headache
- tiredness
- muscle aches
- feeling unwell (malaise)

These are not all of the possible side effects of FLUCELVAX. You can ask your healthcare provider for a complete list of possible side effects.

Ask your healthcare provider for advice about any side effects that concern you. You may report side effects to the Vaccine Adverse Events Reporting System (VAERS) by calling 1-800-822-7967 or by going to http://vaers.hhs.gov.

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Vaccines at 1-877-683-4732 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.

NOVARTIS VACCINES AND DIAGNOSTICS

FLUCELVAX®
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RETHINK FLU.

Novartis Vaccines and Diagnostics, Inc.
East Hanover, New Jersey 07936-1080

August 2013

149531

FLUCELVAX (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
2013-2014 Formula
Initial U.S. Approval: 2012

BRIEF SUMMARY: See package insert for full prescribing information.

1 INDICATIONS AND USAGE

FLUCELVAX® is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine

FLUCELVAX is approved for use in persons 18 years of age and older.

4 CONTRAINDICATIONS

Do not administer FLUCELVAX to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine [*see Description (11) in the full prescribing information*].

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated. If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUCELVAX should be based on careful consideration of the potential benefits and risks.

5.2 Latex

The tip caps of the pre-filled syringes may contain natural rubber latex which may cause allergic reactions in latex-sensitive individuals. [*see Description (11) in the full prescribing information*]

5.3 Preventing and Managing Allergic Reactions

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

5.4 Altered Immunocompetence

After vaccination with FLUCELVAX, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response. [See *Concurrent use with Immunosuppresive Therapies* (7.2)]

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLUCELVAX may not protect all vaccine recipients against influenza disease.

6 ADVERSE REACTIONS

Overall, the most common (≥10 %) solicited adverse reactions occurring in adults 18 to 64 years of age within 7 days of vaccination with FLUCELVAX were pain at the injection site (28%), erythema at the injection site (13%), headache (16%), fatigue (12%), myalgia (11%) and malaise (10%). The most common (≥10%) solicited adverse reactions occurring in adults 65 years of age and older within 7 days of vaccination were erythema at the injection site (10%), fatigue (11%), headache (10%) and malaise (10%).

6.1 Clinical Trials Experience

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

The safety of FLUCELVAX was evaluated in seven randomized, controlled studies conducted in the US, Europe and New Zealand. The safety population includes 5709 adults 18 through 64 years of age and 572 adults 65 years of age and older.

In all studies, solicited local injection site and systemic adverse reactions were collected from subjects who completed a symptom diary card for 7 days following vaccination.

One of the 7 clinical trials was a randomized, double-blind, placebo-controlled study that evaluated a total of 11376 subjects: FLUCELVAX (N=3813), placebo (N=3894) and another influenza vaccine. The population was 18 through 49 years of age (mean 32.8 years), 55% were female and 84% were Caucasian. The safety data observed for FLUCELVAX and placebo are summarized in Table 1.

Table 1: Solicited Adverse Reactions in the Safety Population Reported Within 7 Days of Vaccination in Study 1*

	Adults 18 through 49 Years	
	Percentages (%)	
	FLUCELVAX N=3813	Placebo N=3894
Local adverse reactions		
Injection site pain	30	10
Erythema	13	10
Induration	6	3
Swelling	6	3
Ecchymosis	4	4
Systemic adverse reactions		
Headache	15	15
Fatigue	10	10
Myalgia	12	7
Malaise	8	6
Chills	6	6
Arthralgia	3	3
Sweating	3	3
Fever (≥38° C)	1	<1

* NCT00630331

Study 2 was a randomized, double-blind study comparing FLUCELVAX (N=1330) to a U.S. licensed comparator (N=1324) in adults 18 years of age or older. The mean age was 43.7 years of age for adults 18 to 64 years of age and 71.3 years of age for adults 65 years of age and older; 57% of subjects were female and 100% were Caucasian. The safety data observed are summarized in Table 2.

Table 2: Solicited Adverse Reactions in the Safety Population Reported Within 7 Days of Vaccination in Study 2*

	Adults 18 through 64 Years		Adults 65 Years of Age and Older	
	Percentages (%)			
	FLUCELVAX N=821	Comparator** N=841	FLUCELVAX N=509	Comparator** N=483
Local adverse reactions				
Injection site pain	20	15	8	4
Erythema	14	15	10	11
Induration	6	6	5	4
Swelling	4	4	4	2
Ecchymosis	3	3	4	4
Systemic adverse reactions				
Headache	12	11	10	11
Fatigue	11	11	11	13
Myalgia	7	8	6	8
Malaise	11	11	10	11
Chills	4	4	3	4
Arthralgia	5	5	6	7
Sweating	5	4	7	8
Fever (≥38° C)	1	1	<1	1

* NCT00492063

**AGRIFLU

Unsolicited adverse events, including serious adverse events (SAEs), were collected for 21 days after vaccination in five studies. In adults 18 through 64 years of age (N=4038), 13% (284 out of 2266) of subjects who received FLUCELVAX and 13% (224 out of 1772) of subjects who received a U.S. licensed comparator vaccine reported at least one unsolicited adverse event within 21 days after vaccination. The most commonly reported unsolicited adverse events after FLUCELVAX vaccination were rhinitis (3%), headache (2%) and oropharyngeal pain (2%). In adults 65 years of age and older (N=2013), 11% (110 out of 997) of subjects who received FLUCELVAX and 9% (95 out of 1016) of subjects who received a U.S. licensed comparator vaccine reported at least one unsolicited adverse event within 21 days after vaccination. Within this age group, the most commonly reported

unsolicited adverse events after FLUCELVAX vaccination were rhinitis (3%) and cough (2%). In both age groups, all other unsolicited adverse events were reported in 1% or less of subjects.

In the seven controlled studies of FLUCELVAX, the rates of serious adverse events were collected for 21 days in two studies and for 6 to 9 months in five studies. The rates (in all seven controlled studies) of serious adverse events among adults 18 through 64 years of age were 1% (84 out of 6388) in groups that received FLUCELVAX, 1% (55 out of 5745) in groups that received US licensed comparator vaccines and 1% (37 out of 3894) in groups that received placebo. The rates of serious adverse events among adults 65 years of age and older were 4% (36 out of 997) in groups that received FLUCELVAX and 4% (44 out of 1016) in groups that received a US licensed comparator vaccine.

6.2 Postmarketing Experience
There are no available postmarketing safety data with FLUCELVAX.

7 DRUG INTERACTIONS

7.1 Concomitant use with Other Vaccines
No data are available to assess the concomitant administration of FLUCELVAX with other vaccines.

If FLUCELVAX is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at different injection sites. Do not mix FLUCELVAX with any other vaccine in the same syringe or vial.

7.2 Concurrent use with Immunosuppressive Therapies
Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to FLUCELVAX. [See *Altered Immunocompetence* (5.4)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category B: A reproductive and developmental toxicity study has been performed in rabbits with a dose level that was approximately 15 times the human dose based on body weight. The study revealed no evidence of impaired female fertility or harm to the fetus due to FLUCELVAX. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

In a reproductive and developmental toxicity study, the effect of FLUCELVAX on embryo-fetal and post-natal development was evaluated in pregnant rabbits. Animals were administered FLUCELVAX by intramuscular injection 3 times prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL/rabbit/occasion (approximately 15-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, embryo-fetal development, or post-natal development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

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

8.4 Pediatric Use
Safety and effectiveness have not been established in children less than 18 years of age.

8.5 Geriatric Use
Of the total number of subjects who received one dose of FLUCELVAX in clinical studies (6711), 9% (572) were 65 years of age and older and 2% (140) were 75 years or older.

The majority of local and general adverse events were reported less frequently in adults 65 years of age and older as compared to adults <65 years of age. [*See Adverse Reactions (6.1)*]

Antibody responses to FLUCELVAX were lower in the geriatric (adults 65 years and older) population than in younger subjects. [*see Clinical Studies (14.3) in the full prescribing information*]

Manufactured by: Novartis Vaccines and Diagnostics GmbH
D-35006
Marburg, Germany

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rotavirus fragment[10] and flagellin isolated from a salmonella species.[11] Interestingly, while antibodies specific for M2e rarely occur as a natural response to infection with influenza A virus, animal and human studies have shown it is possible to induce them through vaccination.

Despite the panoply of influenza vaccine choices, influenza remains a serious public health threat.

• *Nucleoprotein (NP).* NP has been included together with M2e or other matrix protein in several vaccine candidates. While NP induces an antibody response, it is a vigorous CD8+ T-cell response in both mice and humans that is thought to account for evidence of protective immunity.[12,13]

Active vaccine development programs are scattered across university-based laboratories and start-up biopharmaceutical firms such as VaxInnate, Okairos, BiondVax, FluGen and Immune Targeting Systems. But despite universal agreement about the overwhelming need, to date, most large manufacturers of seasonal influenza vaccines have hesitated to make a major commitment to develop a universal flu vaccine.

Putting Progress in Perspective

Beginning a decade ago with the emergence of a highly pathogenic avian flu virus, worries about a potential pandemic helped spur a flurry of research activity focused on development of a universal flu vaccine. By the end of the last decade, cautious optimism was being expressed at research conferences that the first such vaccine could be available in as little as five years. This optimism has been tempered, however, by results of a number of early-stage clinical trials documenting evidence of poor cross-protection or weak immunogenicity of candidate HA- and M2e-based vaccines.[14]

Adding another note of caution, this year, FDA scientists described their work with a pig flu vaccine that induced highly cross-reactive antibodies against the HA stem region of a different subtype, resulting in enhanced — not attenuated — severe respiratory disease. The agency warned that universal flu vaccines that target the HA stem region "might enhance influenza disease rather than prevent it."[15] Clearly, there are more potential pitfalls ahead for those working in this complex area of vaccine research.

There is a consensus that solving the puzzle of the influenza virus' extraordinary evolutionary capacity to escape human immunity will require much more basic and applied research. Everyone agrees on the need for a universal flu vaccine. A key question going forward is whether and when government and industry will commit sufficient resources to succeed at what by any measure is a Herculean challenge. ❖

References

1. Influenza activity – United States, 2012-13 season and composition of the 2013-14 influenza vaccine. *MMWR* 2013 Jun 14;62(23):473-9.
2. U.S. Centers for Disease Control and Prevention (CDC). What you should know for the 2013-2014 flu season. Accessed 9/4/2013 at www.cdc.gov/flu/about/season/flu-season-2013-2014.htm.
3. Szabo L and Weise E. USA needs more effective flu shots, experts say. *USA Today* (January 12, 2013). Accessed 8/22/2013 at www.usatoday.com/story/news/nation/2013/01/11/flu-strains-vaccine/1827677.
4. Fauci A. Better flu vaccine on the horizon (September 3, 2013). Accessed 9/5/2013 at m.cnn.com/primary/cnnd_fullarticle?topic=newsarticle&category=cnnd_health&articleId=cnn/2013/09/03/health/better-flu-vaccine-fauci&cookieFlag=COOKIE_SET.
5. Li Y, Myers JL, Bostick DL, et al. Immune history shapes specificity of pandemic H1N1 influenza antibody responses. *J Exp Med* 2013 Jul 29;210(8):1493-500.
6. Ma W, Kahn RE and Richt JA. The pig as a mixing vessel for influenza viruses: Human and veterinary implications. *J Mol Genet Med* 2009 Jan;3(1):158-66.
7. Steel J, Lowen AC, Wang TT, et al. Influenza virus vaccine based on the conserved hemagglutinin stalk domain. *Bio* 2010;1:e00018-10.
8. Ekiert DC, Bhabha G, Elsliger MA, et al. Antibody recognition of a highly conserved influenza virus epitope. *Science* 2009;324:246-51.
9. Gilbert SC. Advances in the development of universal influenza vaccines. *Influenza Other Respi Viruses* 2013 Sep;7(5):750-8.
10. Andersson AM, Håkansson KO, Jensen BA, et al. Increased immunogenicity and protective efficacy of influenza M2e fused to a tetramerizing protein. *PLoS One* 2012;7(10):e46395.
11. Turley CB, Rupp RE, Johnson C, et al. Safety and immunogenicity of a recombinant M23-flagellin influenza vaccine (STF2.4xM2e) in healthy adults. *Vaccine* 2011 Jul 18;29(32):5145-52.
12. Carragher DM, Kaminski DA, Moquin A, et al. A novel role for non-neutralizing antibodies against nucleoprotein in facilitating resistance to influenza virus. *J Immunol* 2008;181:4168-76.
13. Zhou D, Wu TL, Lasaro MO et al. A universal influenza A vaccine based on adenovirus expressing matrix-2 ectodomain and nucleoprotein protects mice from lethal challenge. *Mol Ther* 2010 Dec;18(12):2182-9.
14. Wang L, Zhang H, Compans RW, et al. Universal influenza vaccine – short review. *J Immunol Clin Res* 2013 Aug 7;1:1003.
15. U.S. Food and Drug Administration. FDA-led study describes mechanism potentially responsible for respiratory side effect associated with a pig influenza vaccine. Accessed 9/3/2013 at www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm366625.htm.

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Credit to Luke Noll, Director of Vaccine Product Sales at FFF Enterprises, for contributing helpful input for this article.

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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PIDD: A Physician's Perspective

Dr. Marc Riedl, who has specialized in treating PIDD for 12 years, explains why diagnosis is so difficult, and treatment needs and options.

BY TRUDIE MITSCHANG

Dr. Marc Riedl has specialized in treating primary immune deficiency patients for more than 12 years.

MARC RIEDL, MD, MS, is associate professor of medicine in the Division of Rheumatology, Allergy & Immunology at the University of California, San Diego.

BSTQ: Why is diagnosis of PIDD so difficult?

Dr. Riedl: Studies have shown that PIDD patients go many years without proper diagnosis. One reason is that the symptoms of PIDD can be quite broad. Most patients get reoccurring infections that are troublesome but not necessarily serious, including chronic ear and sinus infections. The second reason is that many providers are simply not familiar with the type of testing that needs to be done regarding PIDD; you need to know what to look for and what lab to use.

BSTQ: You advocate a team approach when it comes to treating PIDD patients. Can you explain that philosophy?

Dr. Riedl: A team approach is needed during treatment of PIDD because the immune system has so many different components. Patients may require a pulmonary doctor, GI specialist and an immunologist, in addition to a primary care physician, and it is critical that these providers consult with one another. Then, there are nurses who administer IV treatments, pharmacists who need to manage the various prescriptions and potential drug interactions, and the caregivers who interact with patients on a daily basis. Communication and collaboration can go a long way toward improving the quality of life for immune deficient patients.

BSTQ: For those not familiar with immune globulin (IG) therapy, can you briefly explain the benefits?

Dr. Riedl: IG therapy reduces the frequency of infections and can significantly improve the quality of life for PIDD patients. Intravenous IG (IVIG) replacement in PIDD has been shown to prevent serious/recurrent infections because higher IgG levels can be obtained through IV administration. IG therapy can result in fewer doctor visits and fewer days off work and school.

BSTQ: What is happening in the area of research regarding treatment for PIDD?

Dr. Riedl: Current research falls into two bins. One is using treatments we have and finding ways to make them more tolerable and more effective. That includes looking at the benefits and side effects of antibody therapy and IG therapy. In the second bin, you find the work that is being done to try to repair the immune systems of these patients such as gene therapy, bone marrow transplants and stem cell transplants. We are seeing exciting breakthroughs in genetic and genomic technology, but the work is ongoing and slow because many of these procedures can be dangerous. For example, a severely ill PIDD patient could be helped by a bone marrow transplant, but there is a mortality risk associated with the procedure. I think we are seeing a lot of progress though. ❖

PIDD: Signs, Symptoms & Treatments

How do physicians know when to suspect a primary immune deficiency disease (PIDD)? According to the Jeffrey Modell Foundation, some warning signs include:

- Four or more new ear infections within one year
- Two or more serious sinus infections within one year
- Two or more months on antibiotics with little effect
- Two or more pneumonias within one year
- An infant's failure to gain weight or grow normally
- Recurrent deep-skin or organ abscesses
- Persistent thrush in mouth or elsewhere on the skin after age 1
- Need for intravenous antibiotics to clear infections
- Two or more deep-seated infections
- A family history of PIDD

There are several treatments commonly used to improve the function of a PIDD patient's immune system:

- Immune globulin infusions to support the immune system with additional antibodies
- Antibiotics that either target a specific infection or act as a preventive treatment
- Anti-inflammatories like prednisone, a synthetic corticosteroid

PIDD: A Patient's Perspective

Symptoms of immune deficiency began when Dona Darr's daughter, Emily, was just a toddler. What started as an ear infection turned into nearly a decade-long quest for an accurate diagnosis.

PRIMARY IMMUNODEFICIENCY disease (PIDD) is an umbrella term encompassing nearly 200 genetic disorders that feature an absent or diminished immune system. PIDD affects as many as 500,000 Americans and 10 million people worldwide, but is often difficult to diagnose. One of the reasons is explained in a theme adopted by the Immune Deficiency Foundation: "Think zebra." The term derives from a medical school adage: "When you hear hoofbeats, you see horses, not zebras," which encourages physicians to look for the likeliest possibilities when making a diagnosis. PIDD patients are considered "zebras" in the medical world.

While many PIDD symptoms present themselves in early childhood, on average, it takes between nine and 12 years from the beginning of symptoms to make a diagnosis. This was certainly the case with the Darr family.

Misdiagnosis: It Must Be Day Care

Dona Darr's world changed for the better in 2003, when her daughter Emily was born. A healthy, happy baby, Emily was a blessing from the start. When her daughter was 18 months old, Dona made the emotionally difficult decision to enroll Emily in day care. An outgoing child, Emily made "fwends" quickly, and Dona was relieved things were going so well. Then Emily got the first of seven recurrent ear infections, and Dona panicked. "Her pediatrician said it was normal for a child in day care to be sick a lot, but seven infections in four months seemed excessive," says Dona. "I knew something wasn't right."

On the advice of friends, Dona took Emily to an ear, nose and throat specialist. After she provided the physician with her daughter's medical history, the doctor looked her in the eye and asked if Emily had been tested for immune deficiency. "I was stunned," says Dona. "The following month, we went back to the pediatrician for blood work, and I felt like the most horrible mother as I held her little body down while they drew blood. Little did I know that this procedure would become a common occurrence throughout her life."

Two weeks later, the results came in. It was confirmed that Emily's IgG levels were low, making her more susceptible to infections and in danger of serious complications if she contracted influenza or pneumonia. The treatment plan? "Just call if she gets sick, and treat viral infections as soon as possible."

Emily Darr was in day care when she first started experiencing recurrent infections. Yet, although it was found that she had low IgG levels, Emily was not diagnosed with IgG subclass deficiency until she was 10 years old. Thanks to the persistence of her mother, Dona, to seek out an immunologist to get the correct diagnosis, Emily is now being treated for her condition.

The Eight-Year Journey

The next two years were filled with doctor appointments and trips to the ER. One misdiagnosis landed Emily in the hospital with pneumonia. When it happened a second time, Dona decided to change doctors. During a consultation with her new pediatrician, Dona heard the term "immunologist" for the first time, but based on Emily's blood work, she was unable to get a referral. Countless strep and viral infections later, Dona began researching her daughter's symptoms on the Internet, and what she learned astounded her. There were thousands of other patients with symptoms just like Emily's; she was not alone, and it was time to see an immunologist. "If no doctor would refer us, I decided I would refer us myself," she says. "Eight years from the start of our journey, my now 10-year-old daughter was close to a diagnosis. We found an immunologist who started looking for the 'zebra,' instead of the horse."

Emily's diagnosis was IgG subclass deficiency with specific antibody deficiency. Her treatment plan includes prophylactic antibiotic along with yearly pneumovax and meningococcal vaccines, with monitoring and testing every three months. If breakthrough infections occur, her immunologist may consider intravenous immune globulin therapy, a common treatment and effective for PIDD.

"Emily's life is forever changed and may include a future filled with doctors, hospitals, medications and labs," says Dona. "But she is strong and resilient. I am so glad I never strayed from that gut feeling and that I kept fighting to get her help." ❖

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

BioResearch

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

Immunogenicity, Reactogenicity and Safety of Quadrivalent and Trivalent Influenza Vaccines

A total of 4,659 adults aged 18 years or older were randomized to receive a single dose of inactivated quadrivalent influenza vaccine (IIV4) from one of three production lots or an inactivated trivalent influenza vaccine (IIV3) containing either a B/Victoria or B/Yamagata strain. The objectives were to evaluate the immunogenicity, reactogenicity and safety of both formulations, as well as lot-to-lot consistency of IIV4. A priori, non-inferiority for IIV4 against IIV3 for the three shared strains was considered demonstrated if the 95 percent confidence interval (CI) upper limit for the geometric mean titer (GMT) ratio was less than or equal to 1.5 and for the seroconversion difference was less than or equal to 10 percent.

Consistent immunogenicity was demonstrated for all three IIV4 lots. IIV4 was non-inferior to IIV3 for the shared vaccine strains (A/H1N1, A/H3N2 and the shared B strain) and, as expected, was superior for the added alternate-lineage B strains. IIV4 elicited robust immune responses against all four vaccine strains, with seroconversion rates of 77.5 percent (A/H1N1), 71.5 percent (A/H3N2), 58.1 percent (B/Victoria) and 61.7 percent (B/Yamagata). The reactogenicity and safety profile of IIV4 was consistent with IIV3.

The investigators concluded that IIV4 provided superior immunogenicity for the additional B strain compared with IIV3, without interfering with antibody responses to the three shared antigens or affecting safety.

Kieninger D, Sheldon E, Lin Wy, et al. Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine: a phase III, randomized trial in adults aged >=18 years. BMC Infect Dis *2013 Jul 24;13(1):343 [Epub ahead of print]*

Intravenous Immunoglobulin (Privigen) Effective, Well-Tolerated as Therapy for Chronic Inflammatory Demyelinating Polyneuropathy

In a prospective, multicenter, single-arm, open-label Phase III study, 61 percent of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) responded to induction and maintenance therapy with a 10% liquid human intravenous immunoglobulin (IVIG) (Privigen, CSL Behring), with response defined as improvement of greater than or equal to 1 point on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale. Patients received a single induction dose of Privigen (2 g/kg body weight) and up to seven maintenance doses of 1 g/kg each at three-week intervals. Of 31 screened patients, 28 were enrolled, including 13 (46.4 percent) who had previously been treated with IVIG.

At completion of this study, 76.9 percent of IVIG-pretreated patients were responders, in contrast to a response rate of 46.7 percent in IVIG-naïve patients. The median INCAT score improved from 3.5 (95 percent confidence interval, 3.0 to 4.5) points at baseline to 2.5 (1.0 to 3.0) points at completion. Improvements in the mean maximum grip strength (66.7 versus 80.9) and the median Medical Research Council sum score (67.0 versus 75.5) were also observed. Of 108 adverse events, 95 were mild or moderate in intensity and resolved by the end of the study.

The authors concluded that Privigen proved efficacious and well-tolerated as induction and maintenance treatment in patients with CIDP.

Léger JM, De Bleecker JL, Sommer C, et al. Efficacy and safety of Privigen in patients with chronic inflammatory demyelinating polyneuropathy: results of a prospective, single-arm, open-label Phase III study (the PRIMA study). J Peripher Nerv Syst *2013 Jun;18(2):130-40.*

Safety and Efficacy of Investigational Single-Chain Recombinant Factor VIII Examined in Preclinical Studies

A recombinant factor VIII (rFVIII) featuring a covalent linkage between heavy and light chains and expressed as a single chain molecule has demonstrated "convincing hemostatic efficacy and excellent tolerability" in multiple animal studies, according to CSL Behring researchers. Called "rVIII-SingleChain" (CSL627), this investigational product was designed with the goal of enhancing the pharmacokinetic profile of rFVIII and its binding affinity to von Willebrand factor.

In a tail-clip bleeding model in which observers were blinded, hemophilia A mice were injected with escalating doses (1 to 150 IU/kg) of rVIII-SingleChain, B-domain deleted rFVIII (ReFacto AF) or full-length rFVIII products (Advate, Helixate). Total blood loss and the percentage of animals in which hemostasis occurred were indistinguishable across products. In a thrombosis model, the effect of rVIII-SingleChain on the incidence of thrombus formation was nonsignificant and comparable to B-domain deleted rFVIII at doses up to 500 IU/kg.

In safety and toxicity studies, treatment with rVIII-SingleChain was not associated with anaphylactic reaction or local intolerance, and demonstrated "an excellent overall safety profile." The investigators called for continued investigation of the product in human Phase I/III trials.

Zollner SB, Raquet E, Müller-Cohrs J, et al. Preclinical efficacy and safety of rVIII-SingleChain (CSL627), a novel recombinant single-chain factor VIII. Thromb Res *2013 Jul 5 [Epub ahead of print].*

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BioProducts

New products in the marketplace.

Oncologist Mobile App

The peer-reviewed journal *The Oncologist* has released its newest mobile app to optimize the digital journal experience for cancer physicians. The fully renewed app provides practitioners with dynamic, rich media articles; user-friendly navigation; pre-release print articles; interactive disease awareness and product details; a library of thought-leader videos and roundtable discussions; challenging cases with pro and con perspectives; CME activities; and supplemental issues. The latest release also provides readers the ability to individualize their own content based on a streamlined user profile. European and Chinese editions are available. The app is available on all of the industry standard platforms (iPad, iPhone, Android, Kindle Fire) and can be downloaded free from the Apple app store and the Android marketplace.

American Society of Clinical Oncology, www.asco.org

Digital Temperature Controllers

The new 5R6-900 is an all-in-one thermoelectric module benchtop temperature controller that can be plugged into the wall as a self-contained temperature control system. It is capable of loading currents up to 10A and can be accessed universally, meaning users can access the device wherever they are located. The unit is PC-programmable and easily connects to a computer through the electrically isolated RS232 communications port. Designed for use in universities, science laboratories and any businesses that specialize in temperature control, it features an easy-to-read digital display for controlling functions, including adjusting output voltage and setting the temperature, an auto output shutdown if the sensor is opened or shorted, and high, low and no alarm settings.

Oven Industries, (988) 766-OVEN, www.ovenind.com

Identification and Label Verification Software

The new version of the In-Sight Track & Trace identification and data verification solution for healthcare serialization includes enhancements that address additional requirements for pharmaceutical and medical device manufacturers to achieve unit-level product traceability. The system can be used to decode human-readable text along with 2-D and 1-D barcodes, including Data Matrix, GS1-128, GS1-DataBar, securPharm and Pharmacode. The pre-programmed add-on software package needs little set up through a touch screen or HMI, and it can be easily integrated into third-party serialization software or MES with industrial protocol support and built-in I/O controls. The technical controls needed for FDA 21 CFR Part 11 validation, including secure user authentication and automatic audit trail generation, also are included.

Cognex Corp., (855) 4-COGNEX, www.cognex.com/tracktrace

Neurostimulation Systems

Medtronic has introduced its new RestoreSensor SureScan MRI neurostimulation systems, the first and only implantable neurostimulation (also known as spinal cord stimulation, or SCS) systems, for use in the treatment of chronic, intractable back and/or limb pain that are approved by the U.S. Food and Drug Administration for conditionally safe full-body magnetic resonance imaging (MRI) under specific conditions. Until now, SCS patients referred for a body MRI were denied a scan due to concerns about the system being affected by the large magnetic fields and radio frequency energy involved in MRI. SureScan MRI percutaneous leads are specially designed with enhancements to reduce or eliminate the hazards produced by the MRI environment. The systems also include a proprietary SureScan feature that sets the neurostimulator into an appropriate mode for the MRI environment, enabling radiology departments to confirm a patient's implantable system is safe for MRI scanning.

Medtronic Inc., (800) 328-0810, www.mrisurescan.com/us/index.htm

BioResources

Recently released resources for the biopharmaceuticals marketplace.

Candidate Handbook for Certified Specialty Pharmacist (CSP) Program

Author: Specialty Pharmacy Certification Board

The Specialty Pharmacy Certification Board (SPCB) has released the *Certified Specialty Pharmacist (CSP) Candidate Handbook*, which provides all of the information essential to applying for and maintaining the credential, including the eligibility requirements, examination content outline, testing information, code of conduct, recertification requirements and fees. The handbook is available for download, and SPCB will begin accepting applications for the CSP exams in July. The CSP exam is offered each April and October at testing centers across the U.S.
www.spcboard.org

Circulation iPad App

Author: American Heart Association

Member or nonmember individual subscribers to *Circulation*, the journal of the American Heart Association, are entitled to full-text access via the new iPad app. Articles are written for cardiologists, cardiovascular disease physicians, electrophysiologists, internists, interventionalists and others interested in cardiovascular medicine; subscribers receive 50 issues per year, which include peer-reviewed reports on clinical and laboratory research relevant to cardiovascular disease, as well as editorial features.
circ.ahajournals.org/site/misc/ipad.xhtml

UniFORM Clinical Trials Software App

Evado, a developer of software for clinical trial research, has launched UniFORM, a breakthrough cloud application to streamline clinical trials by allowing the management of information and complex data from a single-page user-interface — regardless of software, format or user device. While the app will eventually be useful for organizations in all sectors, the technology will first be available to enable customers to run accurate and successful studies, clinical trials and patient registries.
www.evado.com

Revised Re-Engineered Discharge Toolkit

The Agency for Healthcare Research and Quality has released the revised Re-Engineered Discharge Toolkit that hospitals can use to lower their rates of preventable readmissions, particularly among patients with limited English proficiency and patients from diverse backgrounds. The toolkit is based on Project RED (Re-Engineered Discharge), a 12-step intervention developed at Boston University Medical Center, which incorporates medication reconciliation, plain-language discharge instructions, patient education, and telephone follow-up to improve transitions of care and decrease the likelihood of readmissions. The updated version also features five additional tools that were absent from the original intervention, including a post-discharge phone call tool with a sample script and a documentation form, and a tool for administering RED to diverse patient populations.
www.bu.edu/fammed/projectred/toolkit.html

2012 Pharmacist Liability: A Ten-Year Analysis

Authors: Healthcare Providers Service Organization and American Pharmacists Association

The *2012 Pharmacist Liability: A Ten-Year Analysis* report contains an analysis of pharmacist professional liability claims and license protection defense claims paid over a 10-year period from Jan. 1, 2002, through Dec. 31, 2011, along with selected highlights from Health Providers Service Organization's 2012 Qualitative Work Profile Survey. Highlights of the report include:

- More than $16 million was paid in indemnity and expenses for professional liability claims on behalf of pharmacists during the 10-year study period.
- Professional liability claims were most likely to involve allegations that the pharmacist dispensed the wrong drug (overdose was the most common patient injury for pharmacist closed claims).
- Seventy percent of paid license protection defense claims resulted in monitoring, education or the issuing of a caution to the pharmacist, while 3 percent of the licensing board's decisions ended the pharmacist's career.
- Ninety percent of survey respondents who experienced a professional liability claim had been in practice for at least 11 years, which substantiates the idea that the likelihood of experiencing a claim increases with the number of years in practice.

The report can be downloaded or ordered as a hard copy.
www.hpso.com/pharmclaimreport2013

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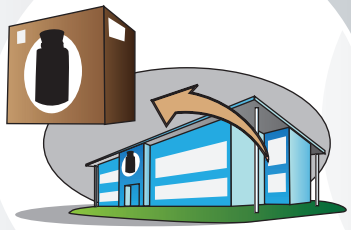
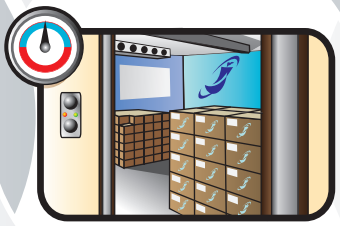


1

PURCHASING

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



2

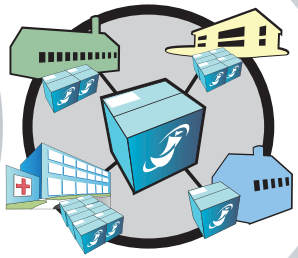
STORAGE

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

3

SPECIALTY PACKAGING

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



4

INTERACTIVE ALLOCATION

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

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

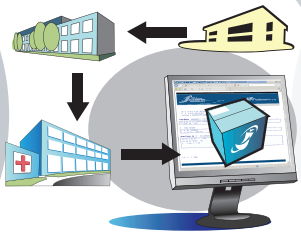
THE MARKETPLACE

5

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

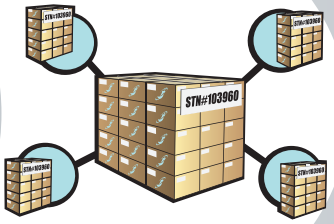
6

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



7

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



8

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

The 8 Critical Steps to Guaranteed Channel Integrity™

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

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

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IVIG Reimbursement Calculator

Medicare Reimbursement Rates*
Rates are effective
October 2013 through December 2013.

Product	Manufacturer	HCPCS	ASP+6% (per gram)
BIVIGAM	Biotest Pharmaceuticals	**	**
CARIMUNE NF	CSL Behring	J1566	$71.50
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$72.16
GAMMAGARD LIQUID	Baxter	J1569	$78.53
GAMMAGARD S/D (Low IgA)	Baxter	J1566	$71.50
GAMMAKED	Kedrion	J1561	$80.94
GAMMAPLEX	Bio Products Laboratory	J1557	$73.56
GAMUNEX-C	Grifols	J1561	$80.94
OCTAGAM	Octapharma	J1568	$62.98
PRIVIGEN	CSL Behring	J1459	$73.08

* Hospital outpatient and physician office settings

Calculate your reimbursement online at www.FFFenterprises.com.

** Refer to Bivigam Coverage and Reimbursement Guide at www.bivigam.com/clientuploads/pdfs/BivigamReimbursementGuide.pdf

IVIG/SCIG Reference Table

Product	Indication	Size	Manufacturer
BIVIGAM Liquid, 10%	IVIG: PIDD	5 g, 10 g	Biotest Pharmaceuticals
CARIMUNE NF Lyophilized	IVIG: PIDD, ITP	3 g, 6 g, 12 g	CSL Behring
FLEBOGAMMA 5% & 10% DIF Liquid	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
GAMMAGARD LIQUID 10%	IVIG: PIDD, MMN SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g	Baxter
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	IVIG: PIDD, ITP, CLL, KD	5 g, 10 g	Baxter
GAMMAKED Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Kedrion
GAMMAPLEX Liquid, 5%	IVIG: PIDD	5 g, 10 g	Bio Products Laboratory
GAMUNEX-C Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
HIZENTRA Liquid, 20%	SCIG: PIDD	5 mL, 10 mL, 20 mL, 50 mL	CSL Behring
OCTAGAM Liquid, 5%	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g	Octapharma
PRIVIGEN Liquid, 10%	IVIG: PIDD, ITP	5 g, 10 g, 20 g, 40 g	CSL Behring

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

2013-2014 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code
Merck / CSL	Afluria (IIV3)	0.5 mL single-dose syringe	9 years and older*	90656
		5.0 mL multi-dose vial		90658
				Q2035 (Medicare)
GlaxoSmithKline	Fluarix (IIV3)	0.5 mL single-dose syringe	3 years and older	90656
	Fluarix (IIV4)	0.5 mL single-dose syringe	3 years and older	90686
	FluLaval (IIV3)	5.0 mL multi-dose vial	3 years and older	90658
				Q2036 (Medicare)
	FluLaval (IIV4)	5.0 mL multi-dose vial	3 years and older	90688
MedImmune	FluMist (LAIV4)	0.2 mL single-use nasal spray	2–49 years	90672
Novartis	Fluvirin (IIV3)	0.5 mL single-dose syringe	4 years and older	90656
		5.0 mL multi-dose vial		90658
				Q2037 (Medicare)
	Flucelvax (ccIIV3)	0.5 mL single-dose syringe	18 years and older	90661
Protein Sciences	Flublok (RIV3)	0.5 mL single-dose vial	18–49 years	90673
				Q2033 (Medicare)
Sanofi Pasteur	Fluzone (IIV3)	0.25 mL single-dose syringe	6–35 months	90655
		0.5 mL single-dose syringe	3 years and older	90656
		0.5 mL single-dose vial	3 years and older	90656
		5.0 mL multi-dose vial	6–35 months	90657
		5.0 mL multi-dose vial	3 years and older	90658
				Q2038 (Medicare)
	Fluzone (IIV4)	0.25 mL single-dose syringe	6–35 months	90685
		0.5 mL single-dose syringe	3 years and older	90686
		0.5 mL single-dose vial	3 years and older	90686
	Fluzone High-Dose (IIV3)	0.5 mL single-dose syringe	65 years and older	90662
	Fluzone Intradermal (IIV3)	0.1 mL single-dose microinjection system	18–64 years	90654

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.

GAMUNEX®-C

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

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2003

WARNING: ACUTE RENAL DYSFUNCTION and FAILURE

See full prescribing information for complete boxed warning.

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

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

GAMUNEX-C is an immune globulin injection (human) 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

----------CONTRAINDICATIONS----------

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity

----------WARNINGS AND PRECAUTIONS----------

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure.
- GAMUNEX-C is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMUNEX-C subcutaneously in patients with ITP.
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome (AMS) has been reported with GAMUNEX-C and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. Monitor patients for hemolysis and hemolytic anemia.
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
- Volume overload
- GAMUNEX-C is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.
- Passive transfer of antibodies may confound serologic testing.

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Talecris Biotherapeutics, Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

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

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

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

Talecris BIOTHERAPEUTICS

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

08939771/08939782-BS
Revised: October 2010

gamunex®-C
immune globulin injection (human), 10%
caprylate/chromatography purified

Evidence based. Patient proven.

Product Features

FDA approved indications[1]:

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Primary immunodeficiency (PI) for both IV and SC administration
- Idiopathic thrombocytopenic purpura (ITP)

Product properties[1]:

- No sugar
- Optimal pH of: (4.0-4.5)
- IgA content: average of 46µg/mL
- Only trace amounts of sodium
- Close to physiologic osmolality: (258 mOsm/kg)

Easy to use[1]:

- Latex-free packaging
- Tamper-evident vials (cap overwrap)
- Vials available in 1, 2.5, 5, 10, and 20 g
- Long 3-year shelf life; room temperature storage*

* Up to 6 months at any time during 36-month shelf life.

Important Safety Information

Gamunex-C, Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified, is indicated for the treatment of primary humoral immunodeficiency disease (PI), idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

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

Gamunex-C is contraindicated in individuals with acute severe hypersensitivity reactions to Immune Globulin (Human). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

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

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

Thrombotic events have been reported in association with IGIV. Patients at risk for thrombotic events may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known or suspected hyperviscosity.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV. The high dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Gamunex-C is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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

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

The most serious adverse reactions in clinical studies were pulmonary embolism (PE) in one subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in one subject (in PI), and myocarditis in one subject that occurred 50 days post-study-drug infusion and was not considered drug related (in ITP).

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

1. GAMUNEX-C package insert. Research Triangle Park, NC: Grifols Therapeutics Inc.; 2010.

For more information: **Grifols, Inc.**
Customer Service: 888 325 8579 Fax: 323 441 7968

Grifols, Inc.
5555 Valley Boulevard, Los Angeles, 90032 CA - USA Tel. 888-GRIFOLS (888 474 3657)
www.grifolsusa.com

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