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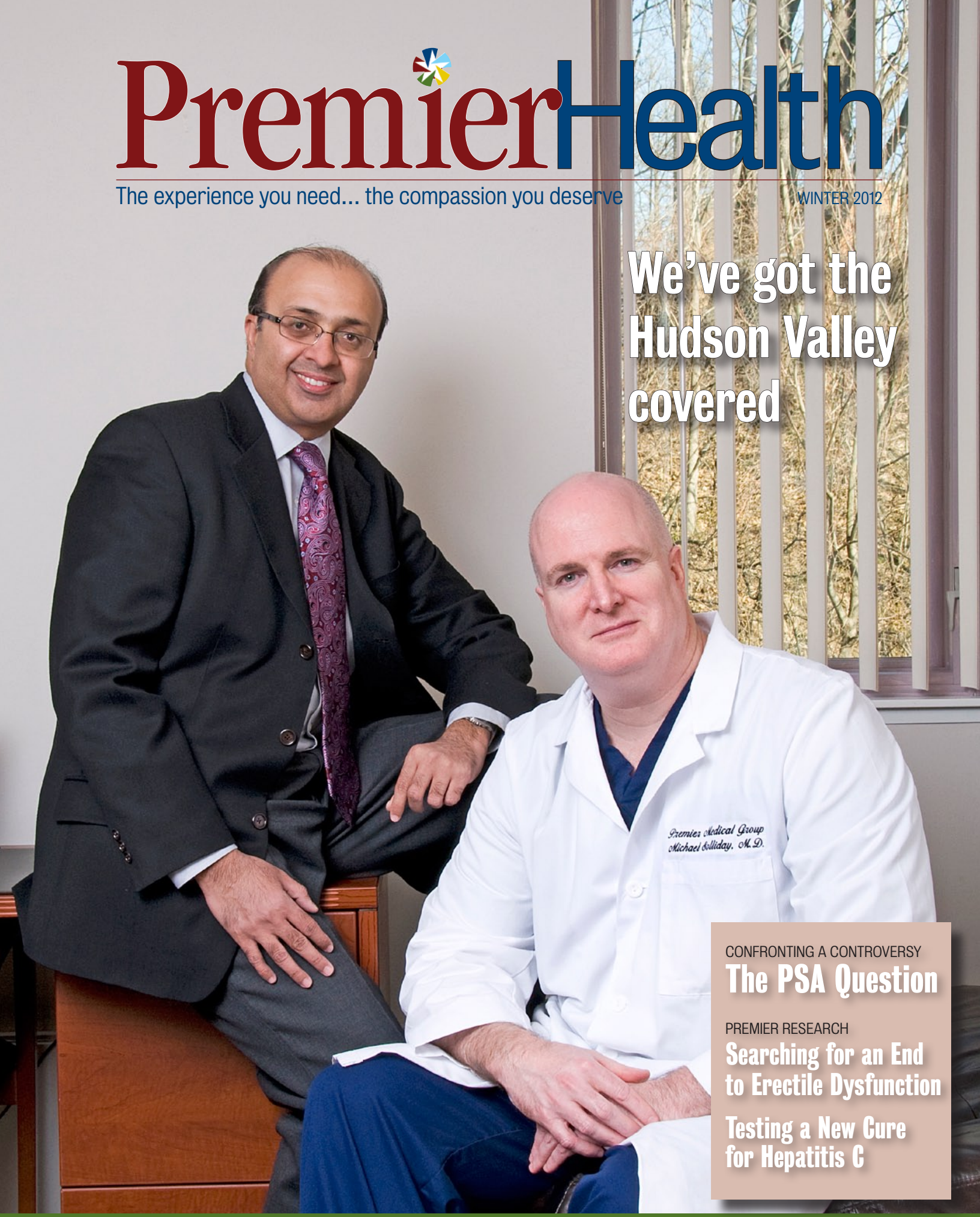

We've got the Hudson Valley covered

CONFRONTING A CONTROVERSY

The PSA Question

PREMIER RESEARCH

Searching for an End to Erectile Dysfunction

Testing a New Cure for Hepatitis C

The magazine of PREMIER *medical group of the Hudson Valley*

LEADING THE WAY TO A HEALTHY HUDSON VALLEY

Premier Medical Group

Premier physicians: Dr. Khurram I. Ashraf *(left)* specializes in endoscopic ultrasound and fine needle aspiration of tumors; Dr. Michael Solliday has a special interest in urological oncology and erectile dysfunction, with a sub-specialty in penile prosthesis and artificial sphincter.

In this issue of Premier Health Magazine we address a controversy relating to prostate cancer that's been making the headlines for several months. If you or your spouse have been thinking about whether or not to get a PSA test, you can't afford to miss the article that begins on page 4.

Premier Medical Group's research departments have been generating excitement, in the GI Division and the Urology Division, with a group of studies that have the potential to significantly change the standard of care for both erectile dysfunction and hepatitis C. *(Read the article begining on page 8).*

In light of new guidelines issued by the Centers for Disease Control and Prevention (CDC) you may have been wondering about getting your children, boys and girls, vaccinated against the human papilloma virus (HPV). We offer an overview of this common infection *(page 10)* to help you make an informed decision.

What do we do with the patient satisfaction surveys you're asked to fill out? You'll find out about that and the GI Division's other continuous quality improvement measures *(page 13)*.

Premier Cares Foundation looks ahead to another pair of flavorful fund raisers. Don't miss out on the Challenge Your Colon Chili Festival *(page 14)*.

PREMIER *medical group*

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A New Practice Administrator for Premier's Urology Division

Effective January 20, 2012, Lorraine O'Donnell takes on the responsibilities of Practice Administrator for the Premier Medical Group Urology Division. In this position she will manage the myriad details that impact the day-to-day operation of the medical practice, from ensuring compliance with laws and guidelines to overseeing billing and personnel and maintaining the integrity of the physical offices.

"She is the natural choice for the position," says Dr. Evan Goldfischer, co-managing partner of the Urology Division. "Lorraine started here nine years ago as a Clinical Research Coordinator, was later promoted to Clinical Research Manager for the department, and was subsequently promoted to Director of Human Resources/Special Projects coordinator.

"What I bring," says O'Donnell, "is my experience. Over nine years I've worked my way up and remain very excited with the growth of the company. And, recognizing that this transition was on the horizon, I went back to school to get my MBA at Marist, with a concentration in healthcare administration."

Lorraine can draw on the stellar performance of Peter Scott, her predecessor in the position, as an example, and all of us at Premier Medical know she is more than up to the task.

Reporting from Medicine's Front Line

In December, 2011, Dr. Salvatore Buffa and Dr. Robert Dean of the GI Division attended the "35th Annual New York Course," a four-day symposium held by The New York Society for Gastrointestinal Endoscopy, the largest regional GI endoscopy society in the U.S.

The course included didactic lectures and live case demonstrations performed by expert faculty and attended via a video feed from Lenox Hill Hospital in the Bronx.

"When any practice members go to these meetings," says Dr. Buffa, "we come back and report to the entire Division about the current research, and equipment and procedural advances that we've learned about. Some of the findings and developments actually lead to changes in our clinical approach, while others are more informational."

Among the take-home points noted by Drs. Buffa and Dean...

• Clarification of the guideline for surveillance of patients with Barrett's Esophagus (BE). BE is a pre-malignant condition, with approximately 10 percent of patients who have it progressing to esophageal cancer. The guidelines now make it clear that these patients should have screening endoscopy at intervals of two years or less.

If low-grade dysplasia is present, the indicated surveillance is every six to 12 months. If high-grade dysplasia is present, focal resection and radio-frequency ablation or esophagectomy are the routine therapies.

• Colonoscopy has decreased mortality from colon cancer, but right-sided colonic lesions are still difficult to detect. Detection of these challenging lesions, the presenters made clear, is aided by adequate colonic preparation on the part of the patient, the ability of the endoscopist to reach the cecum, and careful inspection of difficult folds, including retroflexion. A new device, called the Third Eye Retroscope® may be significantly helpful in visualizing the challenging lesions located in "blind spots" behind the folds of the colon.

• The use of colonic stents for malignant strictures and obstructions permit a one-step operation that doesn't require a temporary colostomy. "We performed just such a procedure last week," says Dr. Buffa. "The problem is, with an obstructing colon cancer or colonic stricture, it's not possible to prep the colon. Previously, the patient would have had surgery, with a colostomy placed for three to six months. Then, when the patient was able to "clean out"—take a prep and have everything pass through—another surgery would have been needed to put them back together.

"With this approach, we can put a stent through the malignant lesion to keep it open and the patient can adequately prep. Then the lesion is removed and the colon reattached, all in a single surgery, without the need for a colostomy. The Course reinforced our conviction that this procedure is becoming the standard of care."

The PSA Question

For several months now, the prostate specific antigen (PSA) test has been the subject of many headlines and news reports. The controversy has centered on the question of whether screening all men with the PSA test actually reduces the overall number of deaths from prostate cancer and whether the benefits of routine screening outweigh the risks.

There is no question that PSA screening can detect prostate cancer about 6 years earlier than a digital rectal exam and 5 to 10 years before symptoms of the disease are recognized. And statistics show that the prostate cancer mortality rate in the US has declined more than 40 percent since the early 1990s, when PSA screening became widespread.

But several large studies conducted to validate and quantify the effects of PSA screening have yielded divergent conclusions and strikingly different interpretations of the data on the part of physicians and scientists.

Though the matter has only recently been widely covered in the media, the physicians of the Urology Division have been investigating and discussing the implications on a daily basis since 2009, when preliminary reports of the studies were first published.

What is the prostate-specific antigen (PSA) test?

Prostate-specific antigen (PSA) is a protein produced by the cells of the prostate gland. The test, first approved by the FDA in 1986, measures the level of PSA in the blood. PSA tests, along with a digital rectal exam (DRE), are given to help detect or monitor prostate cancer.

What do the PSA test numbers mean?

Until recently, the PSA test has been almost uniformly recommended as a routine prostate cancer screening measure for men over age 50 or, for men considered to be at high risk for prostate cancer, beginning at age 40 or 45.

The PSA test reveals the presence or absence of a marker for prostate cancer, it does not serve as a diagnosis of the disease. PSA results are reported as nanograms of PSA per milliliter (ng/mL) of blood. In general, most physicians have considered a total PSA level below 4.0 ng/mL as falling in the "normal" range. A higher concentration suggests an increased risk for the presence of prostate cancer. According to the American Cancer Society, levels between 4.0 and 10.0 ng/mL suggest approximately a 25 percent chance of prostate cancer, while men with levels above 10.0 ng/mL have about a 67 percent chance of prostate cancer being diagnosed upon further examination.

Urologists frequently employ a nuanced approach to PSA levels to increase the test's usefulness as an individualized screening tool. For example, gauging "PSA velocity" — the change in PSA levels over a period of time—can contribute to a more precise estimate of the likelihood of cancer being present or a better understanding of the cancer's aggressiveness.

Why is the PSA test controversial in screening?

The National Cancer Institute describes the PSA controversy as follows:

"Using the PSA test to screen men for prostate cancer is controversial because it is not yet known for certain whether this test actually saves lives. Moreover, it is not clear that the benefits of PSA screening outweigh the risks of follow-up diagnostic tests and cancer treatments.

For example, the PSA test may detect small cancers that would never become life threatening. This situation, called overdiagnosis, puts men at risk of complications from unnecessary treatment. The procedure used to diagnose prostate cancer (prostate biopsy) may cause harmful side effects, including bleeding and infection. Prostate cancer treatments, such as surgery and radiation therapy, may cause incontinence (inability to control urine flow), erectile dysfunction (erections inadequate for intercourse), and other complications. For these reasons, it is important that the benefits and risks of diagnostic procedures and treatment be taken into account when considering whether to undertake prostate cancer screening."

A Urologist's View

by Naeem Rahman, MD

Recently, the US Preventive Service Task Force (USPSTF) released new guidelines regarding prostate-specific antigen (PSA) testing, recommending against PSA screening in men under age 75. While many other medical organizations (e.g., American Cancer Society, National Cancer Comprehensive Network, American Urological Association, among others) continue to advocate PSA screening, I fear that the Task Force's recommendation may potentially be harmful for many men at risk for developing prostate cancer.

Conflicting Studies

The Task Force references two large studies (European and American) published in 2009 to support their statement regarding PSA screening "that if any benefit does exist, it is very small after 10 years." However, these studies have limitations which allow their validity to be questioned. Further, other population-based screening trials and maturation of the aforementioned trials yield different conclusions.

The European Randomized Study for Prostate Cancer (ERSPC) found a 20 percent reduction in prostate cancer deaths over a 9-year period in men who underwent PSA screening. Critics of the positive results of this study suggested that they were associated with "overtreatment," subjecting over 1400 men to screening in order to prevent one death from prostate cancer.

Similarly, the Prostate, Lung, Colon and Ovary Trial (PLCO, a US-based trial assessing PSA screening) published its findings in 2009. With a median follow-up of 6 years, the researchers concluded that no mortality benefit was seen with PSA screening. However, many physicians have found these conclusions to be dubious, as members of the control group (i.e. those who should not have been screened) actually had a 52 percent rate of PSA testing. This significant confounding factor and the relatively short follow-up raise doubts as to the validity of the conclusions.

In contrast (and with much less media attention), a subset analysis from Europe, known as the Göteborg trial, screened patients for a median follow up of 14 years and found a 50 percent reduction in prostate cancer death in those men with PSA testing. Further, only 293 men needed to be screened to prevent 1 death from prostate cancer, a rate in line with many other "proven" screening tests. Of note, the men in this study men were generally younger (median age 56), there was negligible PSA testing in the observation or control arm (3 percent) and the 14 year duration of the study was reflective of the disease process.

As a review of the data published in the *National Cancer Bulletin* points out:

> The substantial mortality reduction in the Göteborg study was achieved even though men in both arms diagnosed with low- to moderate-risk disease received comparable treatments and even though a significant portion of the men in the screening arm who were diagnosed with prostate cancer underwent active surveillance (approximately 40 percent versus approximately 30 percent in the control arm); that is, they chose to forgo definitive treatment, such as surgery or radiation, until there was evidence that their disease was progressing...

Likewise, an analysis of younger, healthier patients in the PLCO study demonstrated a 44 percent reduction in prostate cancer specific mortality. *(continued on next page)*

Evan R. Goldfischer, MD, MBA, FACS

"From my point of view, this current controversy is an opportunity to raise patient-awareness about the PSA test, the risks and benefits, and to reinforce the understanding that it should be used responsibly.

What I'm scared about, quite honestly, is that patients are going to take this the wrong way and say, "Oh, I don't have to get screened for prostate cancer, that's what the new guidelines say." But that's not what the guidelines say.

Just recently I was talking to a patient who had a biopsy right after all these articles came out. And he said to me "I can't believe you did this PSA and this biopsy, look at all this trouble I'll be in. You've made life very confusing."

I told him: "One, I didn't do your PSA, your primary care doctor did; two, your PSA was elevated; three, you're 51 years old and you've got 8 out of 12 cores positive with aggressive cancer. The guidelines talk about active surveillance for non-aggressive forms of cancer. You clearly have the aggressive form of cancer."

At 51 years old, this patient has at least 15-20 years to live. If he doesn't get treated, he's going to die, and prostate cancer is not a good way to go.

It's important to remember that prostate cancer remains the second most common cause of cancer deaths in men."

Prostate cancer is not a monolithic disease and has significant variability in aggressiveness. There are limited and relatively ineffective choices for treating metastatic disease. In fact, survival rates in this category are less than 30 percent. Only early detection will improve these outcomes, and we have seen a 40 percent reduction in prostate cancer mortality since the inception of PSA in the late 1980s.

Parallel concerns of overtreatment are also well-founded, and many patients may never succumb to prostate cancer. Therefore, a patient's decision to pursue treatment should be made in conjunction with his urologist and with full recognition of the risks and benefits involved.

Despite its limitations, and until an alternative test can more accurately predict prostate cancer aggressiveness, PSA screening remains an invaluable tool for all men who are concerned about prostate cancer. To discount PSA screening completely, as the USPTF has advocated, is irresponsible. The urological community will continue to promote PSA testing in the diagnosis, staging, and monitoring of prostate cancer.

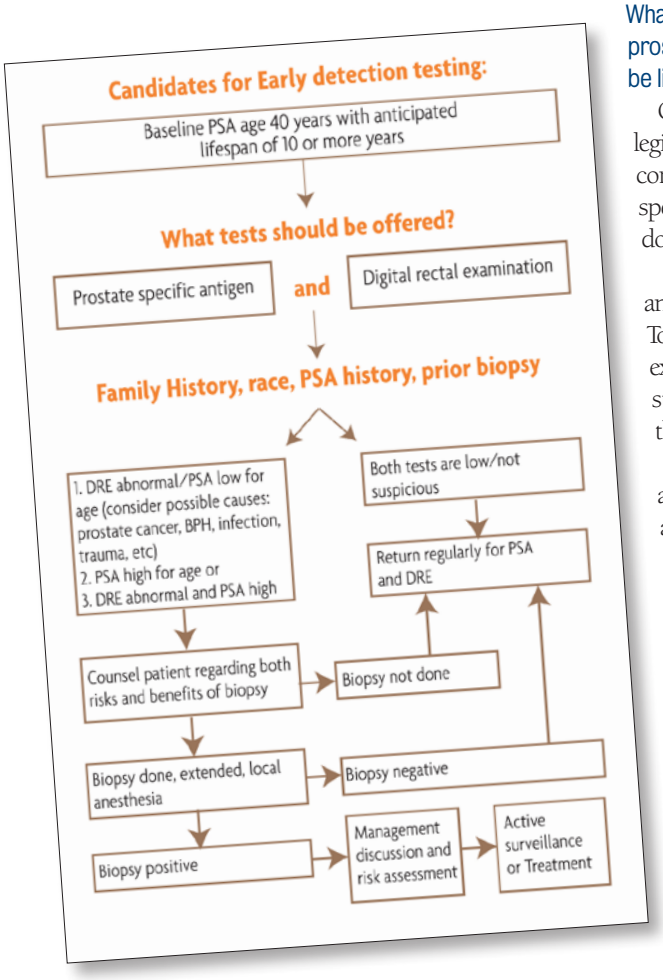
Q & A with Dr. Rahman

Considering its limitations, why do you still feel PSA testing is necessary?

There's a clear correlation between how high a PSA is and the likelihood of cancer, and there's also a correlation between how high a PSA gets and how aggressive the cancer is. For example, with a PSA in the 30s, or 40s, or higher, it would surprising if there was not cancer present.

Those facts in themselves, coupled with the fact that we still have patients who are dying or have significant morbidity, such as pain, from their cancer, speak to the need for screening.

I see several such patients every week, it's not as if these were isolated cases. Patients are having pain because of their cancer, patients are having urinary problems, and patients are seeing their kidneys shut down because of their advanced cancer. These are real clinical scenarios. I think, without PSA screening, we're not going to obviate that. Right now there's no other real way to make a difference in those patient's lives.



What about the concern that some of the prostate cancers diagnosed would not actually be life-threatening?

Overdiagnosis and overtreatment are legitimate concerns. I think if we, as a community of urologists and prostate cancer specialists, discounted that, we would be doing a disservice to our patients.

In the big picture, there is no real black and white here. Every case is different. To make a blanket statement at either extreme, is wrong. But I think a blanket statement advocating not-screening does the more damage of the two.

What we as urologists need to do is acknowledge that not every cancer is aggressive and, in such cases, counsel our patients even more thoroughly on the balance of risk and benefit in treatment. That's where we need to step up to the plate as a community of physicians.

In 2009, The American Urological Association issued a revised "Best Practices Statement" for administering and following up on PSA testing. As the flowchart shows, individualized counseling on risks and benefits of treatment plays a central role in the doctor/patient relationship.

A Partnership in Patient Safety

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Premier Research

Searching for an End to Erectile Dysfunction

Evan R. Goldfischer, MD, MBA, FACS

"I am really excited about the potential of this approach. It could revolutionize the treatment of erectile dysfunction and it could get people off drugs, which are expensive and have side effects."

In April of 2010, a "proof of concept" study published in the journal *European Urology* examined the question, "Can Low-Intensity Extracorporeal Shockwave Therapy Improve Erectile Function?"

The prime cause of most cases of erectile dysfunction (ED) is insufficient blood flow (vascular deficiency) in the penis. The current ED medications (such as Viagra and Cialis), vacuum pumps and injections are all designed to temporarily improve blood flow to the organ's erectile tissue.

The scientists conducting this study structured their proposed new treatment on developments in cardiology and wound healing that indicate therapy employing low-intensity acoustic shockwaves (similar to ultrasound waves) can induce "neovascularization," that is, the creation of new blood vessels.

"Almost every participant gave highly positive feedback, sometimes as early as the second treatment session, with the efficacy still present six months later," the study's authors concluded. "Based on our results, LI-ESWT appears to have the potential to be a rapid and curative therapy for ED… Our short-term results are extremely encouraging, but demand further evaluation."

Premier Medical Group is testing a non-invasive treatment that takes about 15 minutes per visit, involves no medication, is totally painless and promises to cure erectile dysfunction, not just temporarily allay the symptoms.

RIGHT NOW, FURTHER EVALUATION OF THIS PROMISING THERAPY IS BEING CONDUCTED IN POUGHKEEPSIE.

Over the last thirteen years, the Urology Division of Premier Medical Group has earned a reputation for doing excellent research, especially in the area of erectile dysfunction. For that reason, the Division was chosen, as one of only six research sites in the US, to run trials to test the efficacy of LI-ESWT therapy.

"I am really excited about the potential of this approach," says Dr. Evan Goldfischer, Medical Director of the Research Department. "It could revolutionize the treatment of erectile dysfunction and it could get people off drugs, which are expensive and have side effects.

"The drugs and the devices and injection therapy," says Goldfischer, "they're all a little artificial in the sense that you have to plan your sexual activity. If this approach truly works and restores men to normal, which we hope it will, then it will allow for men to have that normal spontaneity again."

"The crux of the treatment," Goldfischer explains, "is neovascularization, that is, the development of new blood vessels. By inducing the development of new blood vessels, we can supply more blood to the penis and, essentially, reverse erectile dysfunction. Since about 90 percent of ED has some vascular component, the vast majority of men with ED could stand to benefit from this therapy."

Men for whom PD5 inhibitors were ineffective because blood flow to the penis was just too deficient may now find that Viagra or Cialis will work. Other patients may discover they no longer need pills or devices for satisfactory sexual activity.

Currently, the use of Low-Intensity Extracorporeal Shockwave Therapy is strictly investigational and not available for general use. There's a protocol with specific criteria defining who is eligible to join. Once a patient is accepted into the trial (for which there is no cost), the protocol calls for two treatments a week over twelve weeks.

As Dr. Goldfischer explains it, "You come in, you lie on a table for a treatment that takes about 15 minutes. During that time about 1500 shockwaves are passed through your penis in different areas. It is not painful, it feels like little taps on the penis. There's no medication involved and no one has required any pain pills, not even a Tylenol afterward. So far there have been no side effects in our treatments."

The Urology Division is still actively looking for men to participate in the trial. Those interested in taking part should call 845-437-5002.

The last year has seen many advances in medications to combat Hepatitis C. But all of them have depended on pegylated interferon, a drug with significant side-effects. The Gastroenterology Division of Premier Medical Group is now conducting trials for a regimen without interferon.

Testing a Hepatitis C Cure that's Easier to Take

Clinical trials currently underway at the GI Division of Premier Medical Group have the potential to "completely change the way we look at hepatitis C," says Dr. Peter M. Varunok, the group's principal investigator for heptatitis studies.

"There are a number of different protocols and medications that are out there being looked at," says Dr. Varunok, "but the most exciting are the non-interferon-based regimens. The study we are doing is for a non-interferon-based regimen with protease and polymerase inhibitors, with and without ribavirin—avoiding the significant side effects of interferon. These direct acting agents (DAAs) are a new class of drug that acts directly on the viral replication site."

For two decades, the standard of care (SOC) therapy for patients infected with the hepatitis C virus (HCV) has included some form of an injectable drug called interferon.

When interferon treatment was first approved by the FDA, in 1991, three injections a week for 48 weeks produced a sustained virological response (SVR) in 9 percent of patients with genotype 1 of the disease, the most common type prevalent in the US, and in 30 percent of patients with genotype 2 or 3. An SVR means that no detectable hepatitic C virus remains in a patient's blood after treatment has ceased.

Adding an oral antiviral drug called ribavirin (in 1998), and using a new form of interferon, called pegylated interferon, led to an SOC that required only one injection a week plus a daily oral medication, and yielded an SVR of 41 percent for genotype 1 and 75 percent for genotypes 2 and 3.

In 2011, the FDA approved two new drugs, the protease inhibitors teleprevir and boceprevir, each of which could be taken along with pegylated interferon and ribavirin. This "triple therapy" has a significantly higher response rate and, for some patients, requires a shorter length of treatment. But the therapy is still difficult to tolerate and would not effect a cure in nearly one million of the four million Americans with hepatitis C.

"We've been limited in who we can treat because of the side effects of the standard treatment," says Dr. Varunok. Some patients with coexisting conditions—psychiatric disorders, low platelet counts, anemia, or autoimmune diseases such as lupus, rheumatoid arthritis and Crohn's disease, for example—cannot be prescribed interferon-based therapy. A signficant number of patients cannot sustain the rigors of the treatment and withdraw from therapy before completion.

INTERIM DATA FROM MID-STAGE TRIALS THAT HAVE BEEN RELEASED BY THE DRUGMAKER SUGGEST THE POSSIBILITY OF VIRAL CURE IN THE 90 PERCENT RANGE, achieved in about half the time of the current standard therapy, and without interferon-related side effects.

"The first arm of our Phase II study is near completion," says Dr. Varunok. "The next step would be to progress to a Phase III trial in which a larger number of patients will be treated."

If the results meet the expectations of many researchers, the new regimen would greatly expand the number of people who could be successfully treated.

Some patients are undoubtedly wondering whether they should delay treatment until a more tolerable, non-interferon-based regimen is available. This may be a reasonable option for some patients, but definitely not for all.

"We're not completely sure when these medications are going to be available," says Dr. Varunok. "The decision to wait for newer medication has to be predicated on the patient's fibrosis (liver scarring) status at this time. Those patients who are at higher risk, with cirrhosis or advanced fibrosis, should not wait but seek treatment now. People with only mild disease on liver biopsy might, after careful discussion with their physicians, make an informed decision to wait."

If it meets researchers' expectations, an experimental drug therapy being studied by the GI Division will provide help to a large population of patients with hepatitis C for whom the current standard of care is ineffective or unavailable.

Peter M. Varunok, MD

"A year ago, a non-interferon-based regimen was thought to be 10 years away. Now, with these new compounds, we expect to have one available much earlier than that. These new medications are likely to become the standard of care and give us the best possible chance of eradicating this virus, because they will be so effective and because we can prescribe them so broadly."

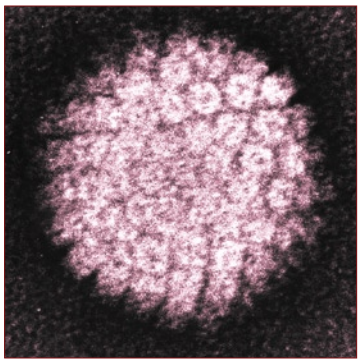
WHAT YOU NEED TO KNOW

About HPV

New guidelines, issued in February by the Centers for Disease Control and Prevention, urge vaccination against the human papilloma virus for all boys aged 11-12. Vaccination for girls aged 11-12 has been recommended since 2006. We offer this review of the facts about HPV to help parents make an informed decision for their children.

Genital human papillomavirus (HPV) is currently the most common sexually transmitted infection in the United States. Approximately 20 million Americans are already infected with HPV and each year another 6 million become newly infected. It's estimated that at least 50 percent of sexually active men and women will get HPV at some point in their lives.

HPV used to be thought of simply as the cause of common skin and genital-area warts. In the late 1970s, however, studies began linking HPV infection to cervical cancer. These studies, which earned their author the Nobel Prize in Medicine, led to further research into the potential dangers of HPV infection. We now know that HPV is responsible for many of the cancers affecting the sexual organs and for oropharyngeal cancers, that is, cancer at the back of the throat, base of the tongue, or of the tonsils.



An electron micrograph of HPV. At least 50 percent of sexually active men and women will be infected with the virus at some point in their lives.
[photo courtesy of U.S. National Institutes of Health]

SIGNS AND SYMPTOMS Since most people with HPV do not experience noticeable symptoms or health problems, they are unaware that they have the infection, and unaware that they are transmitting it. In 90 percent of cases, the virus will be naturally cleared by the body's immune system within about two years. However, when the HPV infection lingers, symptoms and health risks can develop.

Genital warts are the most noticeable symptom, and can appear within weeks or months of contact with an infected partner, even if he or she showed no signs. These warts are caused by a "low-risk" type of HPV, one that does not develop into cancer. Without treatment, some genital warts will go away, some will remain unchanged, while others will grow in size and number. It is not possible to predict the development of individual cases, and the longer genital warts go untreated, the more likely they are to return.

HEALTH RISKS Almost all cases of cervical cancer are caused by HPV. More than 50 percent of vulvar or vaginal cancer, and 95 percent of anal cancers are linked to HPV. A study published this January reveals that HPV is responsible for more oropharyngeal cancers than is tobacco use and estimates that "by 2020, there will be more HPV-positive oral cancers among men than cervical cancers among women in the US."

WHY VACCINATE? There is currently no cure for HPV, just treatment for symptoms. The FDA has approved two HPV vaccines, Gardasil and Cervarix, both highly effective in preventing persistent infection with the "high-risk" HPV types that cause 70 percent of cervical cancers and also effective with HPV-linked cancers at other sites. Gardasil, the only vaccine available to men, is also effective against the HPV types that cause nearly all (90 percent) of genital warts.

To be fully effective, the HPV vaccine must be given before any HPV infection. That's why public health experts recommend it be given in the pre-teen years of 11 or 12.

Michael Solliday, MD

"The rate of STDs appears to be on the rise. We are seeing an increase in the number of genital warts, and national data tells us that about six percent of sexually active adults have experienced them. We remove genital warts, right here in the office, in any number of ways—from cauterization to laser and, occasionally, with medication.

I'm a big fan of the HPV vaccine. Perhaps you don't need it if you're going to be 100 percent responsible, 100 percent of the time. But things happen, and if you get HPV, you may have it for life.

I believe the vaccine is especially important because HPV causes cervical and penile cancers, diseases that can kill you. And the new guidelines that call for boys to be vaccinated make sense. Not only will it cut their risk of throat cancer, males are frequently the vectors for transmitting this virus. We'll have much better control of it if both males and females are vaccinated."

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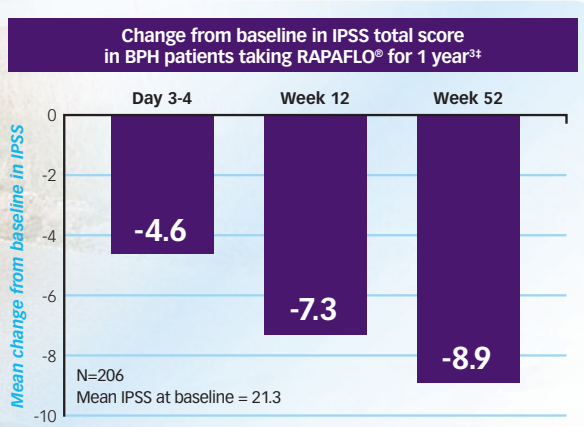
  - Patients taking RAPAFLO® for 1 year had an IPSS§ reduction of ~9 points from baseline[3]



‡*Data from patients who received RAPAFLO® for 12 weeks in a double-blind, placebo-controlled trial and for an additional 40 weeks in an uncontrolled, open-label extension study.*[3]

† *Benign prostatic hyperplasia*
§ *International Prostate Symptom Score*

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Important Safety Information

RAPAFLO® is contraindicated in patients with severe renal impairment (CCr <30 mL/min), severe hepatic impairment (Child-Pugh score ≥10), and with use of strong CYP3A4 inhibitors.

Postural hypotension with or without symptoms (eg, dizziness) may develop when beginning treatment with RAPAFLO®. As with all alpha-blockers, there is a potential for syncope. Patients should be warned of the possible occurrences of such events and should avoid situations where injury could result. RAPAFLO® should be used with caution in patients with moderate renal impairment. Patients should be assessed to rule out the presence of prostate cancer prior to starting treatment with RAPAFLO®. Patients planning cataract surgery should inform their ophthalmologist that they are taking RAPAFLO®.

The most common side effects are retrograde ejaculation, dizziness, diarrhea, orthostatic hypotension, headache, nasopharyngitis, and nasal congestion.

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

Models are for illustrative purposes only.
*IMS Health, National Prescription Audit, December 2010.

www.rapaflo.com

References: 1. Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Rapid efficacy of the highly selective α_{1A}-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. *J Urol*. 2009;181:2634-2640. **2.** Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. *Urology*. 2009;74:1318-1322. **3.** Data on file, Watson Laboratories, Inc.

RAPAFLO® 8 mg (silodosin) capsules

READY. SET. GO.

Watson

RAPAFLO®
(silodosin) capsules

BRIEF SUMMARY

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

RAPAFLO, a selective alpha-1 adrenergic receptor antagonist, is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). RAPAFLO is not indicated for the treatment of hypertension.

CONTRAINDICATIONS

- Severe renal impairment (CCr < 30 mL/min)
- Severe hepatic impairment (Child-Pugh score ≥ 10)
- Concomitant administration with strong Cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir) [*see Drug Interactions*]

WARNINGS AND PRECAUTIONS

Orthostatic Effects

Postural hypotension, with or without symptoms (e.g., dizziness) may develop when beginning RAPAFLO treatment. As with other alpha-blockers, there is potential for syncope. Patients should be cautioned about driving, operating machinery, or performing hazardous tasks when initiating therapy [*see Adverse Reactions and Use in Specific Populations*].

Renal Impairment

In a clinical pharmacology study, plasma concentrations (AUC and C_{max}) of silodosin were approximately three times higher in subjects with moderate renal impairment compared with subjects with normal renal function, while half-lives of silodosin doubled in duration. The dose of RAPAFLO should be reduced to 4 mg in patients with moderate renal impairment. Exercise caution and monitor such patients for adverse events [*see Use in Specific Populations*].

RAPAFLO is contraindicated in patients with severe renal impairment [*see Contraindications*].

Hepatic Impairment

RAPAFLO has not been tested in patients with severe hepatic impairment, and therefore, should not be prescribed to such patients [*see Contraindications and Use in Specific Populations*].

Pharmacokinetic Drug-Drug Interactions

In a drug interaction study, co-administration of a single 8 mg dose of RAPAFLO with 400 mg ketoconazole, a strong CYP3A4 inhibitor, caused a 3.8-fold increase in maximum plasma silodosin concentrations and 3.2-fold increase in silodosin exposure (i.e., AUC). Concomitant use of ketoconazole or other strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonavir) is therefore contraindicated [*see Drug Interactions*].

Pharmacodynamic Drug-Drug Interactions

The pharmacodynamic interactions between silodosin and other alpha-blockers have not been determined. However, interactions may be expected, and RAPAFLO should not be used in combination with other alpha-blockers [*see Drug Interactions*].

A specific pharmacodynamic interaction study between silodosin and antihypertensive agents has not been performed. However, patients in the Phase 3 clinical studies taking concomitant antihypertensive medications with RAPAFLO did not experience a significant increase in the incidence of syncope, dizziness, or orthostasis. Nevertheless, exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events [*see Adverse Reactions and Drug Interactions*].

Caution is also advised when alpha-adrenergic blocking agents including RAPAFLO are co-administered with PDE5 inhibitors. Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension [*see Drug Interactions*].

Carcinoma of the Prostate

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Therefore, patients thought to have BPH should be examined prior to starting therapy with RAPAFLO to rule out the presence of carcinoma of the prostate.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome has been observed during cataract surgery in some patients on alpha-1 blockers or previously treated with alpha-1 blockers. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents; progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs; and potential prolapse of the iris toward the phacoemulsification incisions. Patients planning cataract surgery should be told to inform their ophthalmologist that they are taking RAPAFLO [*see Adverse Reactions*].

Laboratory Test Interactions

No laboratory test interactions were observed during clinical evaluations. Treatment with RAPAFLO for up to 52 weeks had no significant effect on prostate-specific antigen (PSA).

ADVERSE REACTIONS

Clinical Trials Experience

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

In U.S. clinical trials, 897 patients with BPH were exposed to 8 mg RAPAFLO daily. This includes 486 patients exposed for 6 months and 168 patients exposed for 1 year. The population was 44 to 87 years of age, and predominantly Caucasian. Of these patients, 42.8% were 65 years of age or older and 10.7% were 75 years of age or older.

In double-blind, placebo controlled, 12-week clinical trials, 466 patients were administered RAPAFLO and 457 patients were administered placebo. At least one treatment-emergent adverse reaction was reported by 55.2% of RAPAFLO treated patients (36.8% for placebo treated). The majority (72.1%) of adverse reactions for the RAPAFLO treated patients (59.8% for placebo treated) were qualified by the investigator as mild. A total of 6.4% of RAPAFLO treated patients (2.2% for placebo treated) discontinued therapy due to an adverse reaction (treatment-emergent), the most common reaction being retrograde ejaculation (2.8%) for RAPAFLO treated patients. Retrograde ejaculation is reversible upon discontinuation of treatment.

Adverse Reactions observed in at least 2% of patients:

The incidence of treatment-emergent adverse reactions listed in the following table were derived from two 12-week, multicenter, double-blind, placebo-controlled clinical studies of RAPAFLO 8 mg daily in BPH patients. Adverse reactions that occurred in at least 2% of patients treated with RAPAFLO and more frequently than with placebo are shown in Table 1.

Table 1 Adverse Reactions Occurring in ≥ 2% of Patients in 12-week, Placebo-Controlled Clinical Trials

Adverse Reactions	RAPAFLO N = 466 n (%)	Placebo N = 457 n (%)
Retrograde Ejaculation	131 (28.1)	4 (0.9)
Dizziness	15 (3.2)	5 (1.1)
Diarrhea	12 (2.6)	6 (1.3)
Orthostatic Hypotension	12 (2.6)	7 (1.5)
Headache	11 (2.4)	4 (0.9)
Nasopharyngitis	11 (2.4)	10 (2.2)
Nasal Congestion	10 (2.1)	1 (0.2)

In the two 12-week, placebo-controlled clinical trials, the following adverse events were reported by between 1% and 2% of patients receiving RAPAFLO and occurred more frequently than with placebo: insomnia, PSA increased, sinusitis, abdominal pain, asthenia, and rhinorrhea. One case of syncope in a patient taking prazosin concomitantly and one case of priapism were reported in the RAPAFLO treatment group.

In a 9-month open-label safety study of RAPAFLO, one case of Intraoperative Floppy Iris Syndrome (IFIS) was reported.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of silodosin. 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 drug exposure:

Skin and subcutaneous tissue disorders: *toxic skin eruption, purpura*

Hepatobiliary disorders: *jaundice, impaired hepatic function associated with increased transaminase values*

DRUG INTERACTIONS

Moderate and Strong CYP3A4 Inhibitors

In a clinical metabolic inhibition study, a 3.8-fold increase in silodosin maximum plasma concentrations and 3.2-fold increase in silodosin exposure were observed with concurrent administration of a strong CYP3A4 inhibitor, 400 mg ketoconazole. Use of strong CYP3A4 inhibitors such as itraconazole or ritonavir may cause plasma concentrations of silodosin to increase. Concomitant administration of strong CYP3A4 inhibitors and RAPAFLO is contraindicated [*see Contraindications and Warnings and Precautions*].

The effect of moderate CYP3A4 inhibitors on the pharmacokinetics of silodosin has not been evaluated. Concomitant administration with moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil) may increase concentration of RAPAFLO. Exercise caution and monitor patients for adverse events when co-administering RAPAFLO with moderate CYP3A4 inhibitors.

Strong P-glycoprotein (P-gp) Inhibitors

In vitro studies indicated that silodosin is a P-gp substrate. Ketoconazole, a CYP3A4 inhibitor that also inhibits P-gp, caused significant increase in exposure to silodosin. Inhibition of P-gp may lead to increased silodosin concentration. RAPAFLO is therefore not recommended in patients taking strong P-gp inhibitors such as cyclosporine.

Alpha-Blockers

The pharmacodynamic interactions between silodosin and other alpha-blockers have not been determined. However, interactions may be expected, and RAPAFLO should not be used in combination with other alpha-blockers [*see Warnings and Precautions*].

Digoxin

The effect of co-administration of RAPAFLO and digoxin 0.25 mg/day for 7 days was evaluated in a clinical trial in 16 healthy males, aged 18 to 45 years. Concomitant administration of RAPAFLO and digoxin did not significantly alter the steady state pharmacokinetics of digoxin. No dose adjustment is required.

PDE5 Inhibitors

Co-administration of RAPAFLO with a single dose of 100 mg sildenafil or 20 mg tadalafil was evaluated in a placebo-controlled clinical study that included 24 healthy male subjects, 45 to 78 years of age. Orthostatic vital signs were monitored in the 12-hour period following concomitant dosing. During this period, the total number of positive orthostatic test results was greater in the group receiving RAPAFLO plus a PDE5 inhibitor compared with RAPAFLO alone. No events of symptomatic orthostasis or dizziness were reported in subjects receiving RAPAFLO with a PDE5 inhibitor.

Other Concomitant Drug Therapy

Antihypertensives

The pharmacodynamic interactions between silodosin and antihypertensives have not been rigorously investigated in a clinical study. However, approximately one-third of the patients in clinical studies used concomitant antihypertensive medications with RAPAFLO. The incidence of dizziness and orthostatic hypotension in these patients was higher than in the general silodosin population (4.6% versus 3.8% and 3.4% versus 3.2%, respectively). Exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events [*see Warnings and Precautions*].

Metabolic Interactions

In vitro data indicate that silodosin does not have the potential to inhibit or induce cytochrome P450 enzyme systems.

Food Interactions

The effect of a moderate fat, moderate calorie meal on silodosin pharmacokinetics was variable and decreased silodosin maximum plasma concentration (C_{max}) by approximately 18 - 43% and exposure (AUC) by 4 - 49% across three different studies. Safety and efficacy clinical trials for RAPAFLO were always conducted in the presence of food intake. Patients should be instructed to take silodosin with a meal to reduce risk of adverse events.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B. RAPAFLO is not indicated for use in women.

An embryo/fetal study in rabbits showed decreased maternal body weight at 200 mg/kg/day (approximately 13-25 times the maximum recommended human exposure or MRHE of silodosin via AUC). No statistically significant teratogenicity was observed at this dose.

Silodosin was not teratogenic when administered to pregnant rats during organogenesis at 1000 mg/kg/day (estimated to be approximately 20 times the MRHE). No maternal or fetal effects were observed at this dose. Rats and rabbits do not produce glucuronidated silodosin, which is present in human serum at approximately 4 times the level of circulating silodosin and which has similar pharmacological activity to silodosin.

No effects on physical or behavioral development of offspring were observed when rats were treated during pregnancy and lactation at up to 300 mg/kg/day.

Pediatric Use

RAPAFLO is not indicated for use in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In double-blind, placebo-controlled, 12-week clinical studies of RAPAFLO, 259 (55.6%) were under 65 years of age, 207 (44.4%) patients were 65 years of age and over, while 60 (12.9%) patients were 75 years of age and over. Orthostatic hypotension was reported in 2.3% of RAPAFLO patients < 65 years of age (1.2% for placebo), 2.9% of RAPAFLO patients ≥ 65 years of age (1.9% for placebo), and 5.0% of patients ≥ 75 years of age (0% for placebo). There were otherwise no significant differences in safety or effectiveness between older and younger patients.

Renal Impairment

The effect of renal impairment on silodosin pharmacokinetics was evaluated in a single dose study of six male patients with moderate renal impairment and seven male subjects with normal renal function. Plasma concentrations of silodosin were approximately three times higher in subjects with moderate renal impairment compared with subjects with normal renal function.

RAPAFLO should be reduced to 4 mg per day in patients with moderate renal impairment. Exercise caution and monitor patients for adverse events.

RAPAFLO has not been studied in patients with severe renal impairment. RAPAFLO is contraindicated in patients with severe renal impairment [*see Contraindications and Warnings and Precautions*].

Hepatic Impairment

In a study comparing nine male patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), to nine healthy male subjects, the single dose pharmacokinetics of silodosin were not significantly altered in patients with hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment.

RAPAFLO has not been studied in patients with severe hepatic impairment. RAPAFLO is contraindicated in patients with severe hepatic impairment [*see Contraindications and Warnings and Precautions*].

OVERDOSAGE

RAPAFLO was evaluated at doses of up to 48 mg/day in healthy male subjects. The dose-limiting adverse event was postural hypotension.

Should overdose of RAPAFLO lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by maintaining the patient in the supine position. If this measure is inadequate, administration of intravenous fluid should be considered. If necessary, vasopressors could be used, and renal function should be monitored and supported as needed. Dialysis is unlikely to be of significant benefit since silodosin is highly (97%) protein bound.

Watson

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Distributed by: Watson Pharma, Inc., Morristown, NJ 07962 USA
Under license from: Kissei Pharmaceutical Co., Ltd., Nagano, Japan
Address medical inquiries to: WATSON Medical Communications, P.O. Box 1953, Morristown, NJ 07962-1953
800-272-5525
For additional information see:
www.rapaflo.com
or call 1-866-RAPAFLO (727-2356)
Rx Only Revised: November 2009 173761-2 S1109

Measuring Quality

The science of measuring health care performance has made great progress over the last decade. In the GI Division, we methodically review our performance to bring quality improvement to our patients.

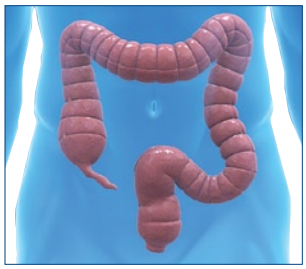
Our ultimate goal in following the expert guidelines and benchmarks for the various procedures and treatments we do is to be certain that any inherent medical risks have been reduced as far as is achievable and that all possible benefits have been maximized.

The patient satisfaction surveys that we ask every person who has had a colonoscopy or endoscopy procedure to fill out, for example, contribute to our "patient experience measures." We regularly collate and examine the results and work to make changes in those few areas where we may not be ranking as high as we'd like.

The data we collect from each physician regarding their clinical practices form the basis of our "process measures" and ensure that we rigorously adhere to the guidelines that yield top quality care.

The American Society for Gastrointestinal Endoscopy publishes a set of 14 quality indicators (QI) for colonoscopy. Meeting or exceeding these indicators means that each of the more than 6,000 colonoscopies performed by the physicians of the GI Division will provide the results we expect and that our patients deserve.

One significant QI is known as the polyp detection rate. Statistical studies have shown that, properly performed, screening colonoscopy will find polyps in approximately 15 percent of women and 25 percent of men over age 50. We actively track the polyp detection rate of each physician. If that rate should temporarily fall out of the expected range, we search for the causes. It could, for example, be that patients are not well-prepared for the procedure: if the colon is not clean, polyps are missed. Whatever the cause, it's addressed as quickly as possible.



"Your job, initially, is to get there [to the cecum]. It's not a struggle, however, to withdraw the scope, and that is when we concentrate on visualizing every millimeter of the colon."

A closely related quality indicator for colonoscopy is known as "withdrawal time." Numerous studies have indicated that physicians who take more than six minutes to withdraw the scope from the *cecum* (the pouch that marks the beginning of the large intestine) to the anus, find more polyps than those who take less than six minutes.

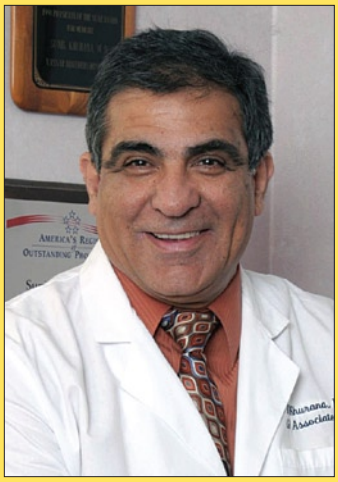
"THE HARDEST THING IN A COLONOSCOPY," SAYS DR. SUNIL KHURANA, "IS TO NAVIGATE THROUGH ALL THE TURNS AND GET TO THE CECUM. Your job initially is to get there, and your concentration is devoted to getting there. It's not a struggle, however, to withdraw the scope, and that is when we concentrate on visualizing every millimeter of the colon."

To help make sure that this quality indicator is rigorously adhered to, the GI Division has invested in specialized software that is attached to the colonoscopy process. "It's important to develop a structure that keeps the process fresh," says Dr. Khurana, "one that doesn't allow the procedure to become too routine. This software reinforces the concept that the physicians must be cognizant of the fact that they need to spend adequate time in visualizing. And, administratively, we are able to review the data and provide oversight."

Combining cognizance with software has led the GI Division to superior adherence to colonoscopy benchmarks, but that's just the beginning. A review of the guidelines is conducted every six months and practice-wide procedures are updated to reflect the latest data. The GI Division makes sure to have a representative at major clinical meetings, and these conference attendees update all the physicians on the latest trends and techniques. Medicine is a work in progress and, at Premier Medical Group of the Hudson Valley, we strive to stay ahead of the curve.

AS PREMIER HEALTH GOES TO PRESS

A NEW STUDY CONFIRMS Colonoscopy SAVES LIVES



Sunil K. Khurana, MD

"The ultimate goal of everything we do is to make a real difference in our patients' lives. For that reason, outcome measures—examining the effects of care—are one of the most important things that we track.

So we are very excited with the conclusions of a major study published in the February 23 issue of the *New England Journal of Medicine* that finds the risk of colorectal cancer mortality is reduced by 53 percent in patients who have had precancerous polyps removed in the course of colonoscopy.

Researchers tracked mortality, for up to 23 years, in a group of patients enrolled in the National Polyp Study. Comparing the death rate from colorectal cancer in the general population with that of the 2602 patients in the study group conclusively showed that colonoscopy and polyp removal increased longevity.

Clearly, screening for colorectal cancer with colonoscopy is worthwhile. Yet only 60 percent of adults are up-to-date on this screening. If more made use of it, more lives would be saved."

TASTY WAYS TO RAISE MONEY FOR A GOOD CAUSE

Our First Celebrity Chef Dinner

On Saturday, November 5, 2011, Premier Cares Foundation hosted its first annual Celebrity Chef Dinner. One hundred and thirty people attended this sold-out event, featuring former executive chef of the White House Walter Scheib at the Poughkeepsie Tennis Club.

Chef Scheib prepared a multi-course dinner featuring a selection of the favorite dishes served during his 1994-2005 tenure at the White House. Carlo Citera and his team from Cosimo's Restaurant Group did an amazing job working in tandem with Chef Scheib to cater the event.

Guests were delighted with insider's tales and culinary insights as they had the chance to be part of history and feast like the presidents.

Premier Cares Foundation offers a special "thank you" to all our sponsors and attendees for their support and enthusiasm. The Foundation is proud to announce that the evening netted over $50,000. Proceeds will be going to support the treatment of patients with prostate or colon cancer in the Hudson Valley.

Sponsors and Dinner attendees helped the Foundation raise $50,000 to support the treatment of patients with prostate or colon cancer.

SAVE THE DATE

Premier Cares Foundation's second annual Celebrity Chef Dinner, entitled "Re-Elect White House Chef Walter Scheib," will be held on Saturday evening, **November 10, 2012.**

Chef Scheib returns to the Hudson Valley during election month, this time preparing a multi-course State Dinner featuring specialty cuisines he prepared for some of the most memorable guests during his tenure at the White House, including Tony Blair, Nelson Mandela and Lady Diana Spencer.

Chef Scheib will be holding a Master Chef cooking class and a small cocktail party for top sponsors of the Premier Cares Foundation fundraiser during the weekend.

PREMIER CARES FOUNDATION

invites you to take part in
Colon Cancer Awareness Day 2012
at our 1st annual

Challenge Your Colon Chili Festival

[CELEBRATING THE CULINARY FLAVORS OF THE HUDSON VALLEY]

Date: Sunday, March 25, 2012 • Time: 12–3 pm

Location: Poughkeepsie Grand Hotel

This family-friendly event will feature local restaurants serving tasting portions of their prize chili recipes and other specialties. There will be music by a local country music band, dancing, chili judging contests, and much more! "Pasta tastings," games and activities will be available for the children.

Funds raised at the Chili Festival will help provide uninsured individuals in our community with free colon cancer screenings.

To register on-line, please visit www.premiercaresfoundation.org

Adults, Food Tastings — $35 Pre-registration/ $40 at the door
Adults over 21, Food & Wine Tastings — $50 Pre-registration/ $55 at the door
Children (12 and under) — $10 Pre-registration/ $15 at the door
(The first 300 people to register will receive a complimentary Chili Festival t-shirt and commemorative tasting mug.)

For more information on registration or sponsorship, please contact
Julie Goldfischer at jgoldfischer@premiercaresfoundation.org or 845.453.1160

Salvatore M. Buffa, MD

"Our first annual "Challenge your Colon" Chili Festival should be a wonderful community event, increasing awareness of colon cancer as well as encouraging surveillance to eliminate this dreaded but preventable disease.

Besides the entertainment activities, many aspects of the event are of an educational nature. There will be booths designed to provide community members with increased knowledge about colon cancer and GI disease; tables offering brochures, videos, and nutritional suggestions; and opportunities to sign up to participate in ongoing research studies.

A highlight of the event will be an essay contest in which entrants tell their stories of having delayed colonoscopic exams due to financial hardship. The selected winners will receive FREE colonoscopies with the physicians and staff at Premier Medical Group of the Hudson Valley. Hearing from some of the winners in person was the most compelling and well received portion of last year's Colon Cancer Awareness Day."

- In a maintenance trial, of the patients who achieved clinical response at week 4, greater proportions of HUMIRA-treated patients, compared to placebo patients, were in clinical remission at week 26 (40% vs 17%, $P<0.001$) and week 56 (36% vs 12%, $P<0.001$)[1]
- HUMIRA can be self-injected at home or almost anywhere, after a physician determines that it is appropriate and after proper training in injection technique. Instruct patients to refer to storage instructions found in the Medication Guide[1]

Indications[1]

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Safety Considerations[1]

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies

Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

Other Serious Adverse Reactions

Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

HUMIRA®
adalimumab

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before HUMIRA use and during therapy. Treatment for latent TB should be initiated prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with HUMIRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA in patients with an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- Exercise caution in patients with chronic or recurrent infection or with underlying conditions which may predispose them to infection, patients who have been exposed to TB, patients with a history of opportunistic infection, or patients who have resided or traveled in regions where TB or mycoses are endemic.
- Patients who develop a new infection should undergo a prompt and complete diagnostic workup, and appropriate antimicrobial therapy should be initiated.
- Drug interactions with biologic products: Concurrent use of anakinra or abatacept with HUMIRA is not recommended, as the combination of anakinra or abatacept with TNF blockers has been associated with an increased risk of serious infections. This risk has also been observed with rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- The risks and benefits of HUMIRA treatment should be considered prior to initiating or continuing therapy in a patient with known malignancy.
- More cases of malignancies were observed among HUMIRA-treated patients compared to control patients in clinical trials.
- Non-melanoma skin cancer (NMSC) has been reported during clinical trials for HUMIRA-treated patients. All patients, particularly those with history of prolonged immunosuppressant or PUVA therapy, should be examined for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use.
- Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration.
- If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after treatment with HUMIRA.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation.
- Exercise caution when considering resumption of HUMIRA therapy after appropriate treatment for HBV.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated in rare cases with new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA in patients with significant hematologic abnormalities.

CONGESTIVE HEART FAILURE

- Worsening or new onset congestive heart failure (CHF) may occur.
- Exercise caution in patients with CHF and monitor them carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome.
- Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (incidence >10%) were: infections (e.g. upper respiratory, sinusitis), injection site reactions, headache, and rash.

Please see Brief Summary of full Prescribing Information on following pages.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: Abbott Laboratories.

HUMIRA®
adalimumab

Abbott
A Promise for Life

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNINGS: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before HUMIRA use and during therapy. Treatment for latent TB should be initiated prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with HUMIRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy. *[See Warnings and Precautions and Adverse Reactions]*

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member. *[See Warnings and Precautions]* Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warnings and Warnings and Precautions]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

(see also Boxed WARNINGS)

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA [*see Warnings and Precautions and Drug Interactions*].

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Anti-tuberculosis therapy should also be considered prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Tuberculosis should be strongly considered in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with HUMIRA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive Fungal Infections

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

Malignancies

The risks and benefits of TNF-blocker treatment including HUMIRA should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 32 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), and plaque psoriasis (Ps), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.38, 0.93) per 100 patient-years among 6694 HUMIRA-treated patients versus a rate of 0.5 (0.28, 1.05) per 100 patient-years among 3749 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 45 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD and Ps, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, and Ps, the rate (95% confidence interval) of NMSC was 0.7 (0.50, 1.11) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.06, 0.56) per 100 patient-years among control-treated patients. All patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF blocker-treated patients compared to control-treated patients. In the controlled portions of 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, and Ps, 3 lymphomas occurred among 6694 HUMIRA-treated patients versus 1 among 3749 control-treated patients. In 45 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD and Ps with a median duration of approximately 0.6 years, including 22,026 patients and over 32,000 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

Hypersensitivity Reactions

In postmarketing experience, anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA in adults, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, HUMIRA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

Clinical Studies Experience

The most serious adverse reactions were:

- Serious Infections [*see Warnings and Precautions*]
- Malignancies [*see Warnings and Precautions*]

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of Studies RA-I, RA-II, RA-III and RA-IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 32 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD and Ps, the rate of serious infections was 4.7 per 100 patient-years in 6694 HUMIRA-treated patients versus a rate of 2.7 per 100 patient-years in 3749 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 45 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD and Ps that included 22,026 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. In a subgroup of 8940 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.07 per 100 patient-years and the rate of positive PPD conversion was 0.06 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.07 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in patients with Crohn's disease with control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with plaque psoriasis with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown. In patients with juvenile idiopathic arthritis, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant methotrexate, the incidence was 6% compared to 26% with HUMIRA monotherapy.

In patients with ankylosing spondylitis, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with rheumatoid arthritis. In patients with psoriatic arthritis, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with rheumatoid arthritis; however, in patients receiving concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis. In patients with Crohn's disease, the rate of antibody development was 3%. In patients with plaque psoriasis, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In plaque psoriasis patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

Other Adverse Reactions

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week. Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated pediatric patients in the juvenile idiopathic arthritis (JIA) trial were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions, Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

HUMIRA was studied in 171 pediatric patients, 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

A total of 45% of children experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in children receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment, non-serious hypersensitivity reactions were seen in approximately 6% of children and included primarily localized allergic hypersensitivity reactions and allergic rash.

Isolated mild to moderate elevations of liver aminotransferases (ALT more common than AST) were observed in children with JIA exposed to HUMIRA alone; liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment.

In the JIA trial, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of children treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK). Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 patients with Crohn's disease in four placebo-controlled and two open-label extension studies. The safety profile for patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 patients with plaque psoriasis in placebo-controlled and open-label extension studies. The safety profile for patients with plaque psoriasis treated with HUMIRA was similar to the safety profile seen in patients with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in plaque psoriasis patients, HUMIRA-treated patients had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Postmarketing Experience

Adverse reactions have been reported during post-approval use of HUMIRA. 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 HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar)

Vascular disorders: Systemic vasculitis

DRUG INTERACTIONS

Methotrexate

Although methotrexate (MTX) reduces the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biologic Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA [*see Warnings and Precautions*]. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information to provide recommendations regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, Crohn's Disease, and plaque psoriasis.

Live Vaccines

Live vaccines should not be given concurrently with HUMIRA *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B - There are no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

Nursing Mothers

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than juvenile idiopathic arthritis (JIA) have not been established.

Juvenile Idiopathic Arthritis In the JIA trial, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age. HUMIRA has not been studied in children less than 4 years of age, and there are limited data on HUMIRA treatment in children with weight <15 kg.

The safety of HUMIRA in pediatric patients in the JIA trial was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Warnings and Precautions]*.

Geriatric Use

A total of 519 rheumatoid arthritis patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

PATIENT COUNSELING INFORMATION

Patients or their caregivers should be provided the HUMIRA "Medication Guide" and provided an opportunity to read it and ask questions prior to initiation of therapy. The healthcare provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

Patient Counseling

Patients should be advised of the potential benefits and risks of HUMIRA. Physicians should instruct their patients to read the Medication Guide before starting HUMIRA therapy and to reread each time the prescription is renewed.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Patients should be counseled about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Patients should be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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SOME MEMBERS OF TEAM PREMIER: *Back row (left to right)*: Ian Flewelling, Jacqueline Woolcock, Patty Sullivan, Theresa Arno, Jenn Coalla; *Middle row:* Donna Hochlowski, Joy Jones; *Front row:* Sandra Wilson, Lisa Gray, Rachel Germano, Adele Lawler, Pam Faulds.