

Summary

A lot of information and a lot of side-effects for these two drugs – over 60 pages of information – a good portion is important for you. You should read about the first part about SLE, also the side-effects of the two drugs.

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Systemic Lupus Erythematosus

WHAT IS SYSTEMIC LUPUS ERYTHEMATOSUS?

Systemic lupus erythematosus is a chronic, often life-long, autoimmune disease that ranges from mild to severe and afflicts mostly women. Systemic lupus erythematosus (SLE) may affect widespread sites, but it most often manifests in the skin, joints, blood, and kidneys. SLE was first described in 1828. Its very name helps define the disease:

- *Systemic* is used because the disease can affect organs and tissue throughout the body.
- *Lupus* is Latin for wolf. It refers to the rash that extends across the bridge of the nose and upper cheekbones and was thought to resemble a wolf bite.
- *Erythematosus* is from the Greek word for red and refers to the color of the rash.

The primary characteristics of the disease are the following:

- Fatigue.
- Joint pain.

- Recurrent injuries in the vessels that course through the body.

WHAT CAUSES SYSTEMIC LUPUS ERYTHEMATOSUS?

Systemic lupus erythematosus is a complex disorder that occurs as a consequence of a number of independent processes and factors, most likely the following:

- An autoimmune response, in which immune factors attack the person's own cells, is central to the disease process.
- A combination of genetic factors that make patients susceptible to the abnormal immune process.
- Environmental factors, such as viruses or sunlight, that assault the body's cells or affect other changes are necessary to trigger the abnormal immune response to begin with.

The Inflammatory Process and Autoimmunity

The Normal Immune System Response. The inflammatory process is a byproduct of the body's immune system, which fights infection and heals wounds and injuries:

- When an injury or an infection occurs, white blood cells are mobilized to rid the body of any foreign proteins, such as a virus.
- The masses of blood cells that gather at the injured or infected site produce factors to repair wounds, clot the blood, and fight any infective agents.
- In the process the surrounding area becomes inflamed and some healthy tissue is injured.
- Under normal conditions, the immune system has other factors that control and limit this inflammatory process.

The Infection Fighters. The primary infection-fighting units are two types of white blood cells: lymphocytes and leukocytes.

Lymphocytes include two subtypes known as *T-cells* and *B-cells*. Both types of cells are designed to recognize foreign invaders, *antigens*, and to launch an offensive or defensive action against them:

- B-cells produce *antibodies* when confronted with an antigen coming from outside the cell. Antibodies are separate agents that can either ride along with a B-cell or travel on their own designed to attack the antigen. The B-cell then develops a "memory" to remember that specific antigen and alert the immune system if it detects it again.
- T-cells also have special receptors attached to their surface that recognize specific antigens.

T-cells, however, are further categorized as killer T-cells or helper T-cells (TH cells).

- Killer T-cells directly attack antigens, such as viruses, that occur in any cells that contains a nucleus.
- Helper T-cells recognize antigens, but their role is two fold. They stimulate B-cells and other white cells to attack the antigen. They also produce *cytokines*, powerful immune factors that have an important role in the *inflammatory process* .

Helper T-Cells. The actions of the helper T-cells are of special interest in this process. For some unknown reason, the T-cells become overactive and mistake the body's own cells as an antigen and trigger a series of immune responses to destroy the false enemy. TH-cells stimulate B-cells to produce antibodies. In this case, however they appear to direct the B-cells to produce *autoantibodies*, which are directed against the body's own cells. Antibodies come in five types: IgM, IgG, IgA, IgD, or IgE. The autoantibody in SLE appears to be derived from IgG.

Autoantibodies. In the majority of patients with SLE, antinuclear antibodies (ANA) are the specific autoantibodies that attack the nucleus and DNA of the patient's healthy cells. Experts have identified two subtypes of ANA that are specific only to SLE patients:

- Anti-double stranded DNA (anti-ds DNA). Anti-ds DNA may play a particularly important role in the process.
- Anti-Sm antibodies.

Other autoantibodies may also be involved:

- Anti-Ro (SSA). These autoantibodies may be involved in the sun-sensitivity experienced by SLE patients.
- Antiphospholipid antibodies. About half of SLE patients also have these antibodies. They attack phospholipids, fatty compounds found in cell membranes throughout the body. Antiphospholipid antibodies increase the risks for blood clots and may be responsible for narrowing of and irregularities in blood vessels and low blood cell counts. Antiphospholipid antibodies are linked with kidney, heart, cerebral, and eye problems in SLE.

Cytokines. TH-cells also secrete or stimulate the production of powerful immune factors called cytokines. In small amounts, cytokines are indispensable for healing. If overproduced, however, they can cause serious damage, including inflammation and cellular injury. They may even be responsible for inflammation that occurs in parts of the body beyond the joints, including fever, shock, and even damage to organs, such as the liver. Certain cytokines called interferons and interleukins play a critical role in SLE by regulating the secretion of autoantibodies by B-cells.

Complement. Another immune factor of high interest in SLE is *complement*. This is comprised of more than 30 proteins and is important for defending and regulating the immune response against foreign cells. Inherited deficiencies in certain complement

components (C1q, C1r, C1s, C4, and C2) have long been associated with SLE. Deficiencies may contribute to SLE in the following manner:

- Complement may protect against autoimmune disease by normalizing *apoptosis*, the natural process by which cells self-destruct. In their absence, then, apoptosis goes awry and leads to the release of *nucleosomes* (collections of DNA and protein) that, in turn, trigger the destructive SLE antinuclear autoantibodies.
- Complement components are also necessary for clearing molecular rubble called *immune complex*. This is the end product of the previous intense immune activity. It consists of autoantibodies and antigens, leftover debris when the battle is over. In the absence of complement, this debris accumulates and is deposited in the kidneys, blood vessels, joints, and other sites where it further incites the immune system to produce inflammation and tissue damage. Deficiencies in an enzyme called Dnase1, which degrades DNA, may be particularly important in the SLE process.

Genetic Defects

Genetic abnormalities, most likely a number of them, are involved to create a propensity for an autoimmune response in the presence of environmental factors, such as viruses or sunlight. One study of SLE patients found defects in four genes that regulate apoptosis, the natural process by which cells self-destruct. Another study has identified an inefficient gene in some SLE patients that promotes the build-up of immune complexes that can cause kidney damage.

HLA. HLA (human leukocyte antigen) is a genetically regulated molecule that traps part of antigens and presents them on the surface of cells for destruction by antibodies and T-cells. It is designed to recognize self- from non-self cells. Those associated with lupus are specific HLAs known as HLA-DR2, -DR3, -A1, -B8, and DMA*0104. Other genetically determined components are also under investigation.

Triggers of the Immune Response

One or more external factors appear to initiate this autoimmune response in genetically susceptible people. SLE triggers include colds, fatigue, stress, oral contraceptives, chemicals, sunlight, and certain drugs.

Viruses. The most likely trigger would be a virus that disrupts the T-cell population. Blood tests reveal that SLE patients are more likely to have been exposed to certain viruses than the general population, but experts have not been able to identify any specific virus as the primary suspect.

Of some interest are studies that have found an association between Epstein-Barr virus (the cause of mononucleosis), cytomegalovirus, and Parvovirus-B19 with SLE. These viruses are very common, however, and in any case, it is unlikely that viruses are the sole cause of SLE, since immune system defects vary widely from patient to patient.

Some research suggests that different viruses may imprint specific types of SLE. For instance cytomegalovirus may affect blood vessels and cause problems such as Raynaud's phenomenon or blood abnormalities, but may not affect the kidney as much.

Sunlight. Ultraviolet (UV) rays found in sunlight are important SLE triggers. When they bombard the skin, they can alter the structure of DNA in cells below the surface. The immune system may perceive these altered skin cells as foreign and trigger an autoimmune response against them. UV light is categorized as UVB or UVA depending on the length of the wave.

- UVB are short waves (280 to 320 nm). The shorter the wavelengths, the more damage they do.
- UVA are longer (320 to 400) nm. (Of interest is research suggesting that UVA wavelengths in the longest range, known as UVA1 (340 to 400), may actually repair DNA and normalize apoptosis and immune responses).

Drug-Induced Lupus. Some people develop lupus after taking certain prescription drugs, such as minocycline. So far 39 drugs in current use have been linked with the onset of lupus. Patients with drug induced lupus recover after ceasing the medication.

Hormones. In general, estrogen enhances antibody production and causes flare-ups while testosterone reduces antibody production. Cytokines, major immune factors that are active in SLE, are directly affected by sex hormones. Women with SLE often have lower levels of several active male hormones (androgens), and some men who are affected by SLE may have abnormal androgen levels.

Silicone Implants. Silicone breast implants have been under intense scrutiny as a possible trigger of autoimmune diseases, including SLE. Most studies are not finding any association except possibly with Sjögren's syndrome. Of concern, however, was one 1999 study of mice in which long time exposure to silicone implants led to the development of arthritis mediated by autoantibodies to collagen. It is not known whether these findings apply to women.

WHO GETS SYSTEMIC LUPUS ERYTHEMATOSUS?

An estimated 500,000 Americans have been diagnosed with systemic lupus erythematosus, although surveys indicate that the prevalence may be much higher. The incidence of the disease has been increasing in recent years, possibly because more physicians have been trained to recognize the syndrome.

Gender

About 90% of lupus patients are women, most of whom are diagnosed when they are in their childbearing ages, a fact that might be explained by hormones. After menopause, women are only two and a half times as likely as men to contract SLE, and flares are uncommon in postmenopausal women who have chronic SLE.

Ethnicity

African-Americans are three to four times more likely to develop the disease than Caucasians and to have severe complications. Hispanics and Asians are also more susceptible to the disease.

Family History

A family history plays a strong role in SLE; a sibling of a patient with the disorder has 20 times the risk as someone without an immediate family member with SLE.

Risk Factors in Children

The disease is rare in childhood. When it does occur, it is often associated with thrombotic thrombocytopenic purpura, a heart condition resulting from abnormally low levels of blood platelets. SLE in children may also be caused by certain medications, including minocycline and zafirlukast.

The Presence of Other Autoimmune Disorders

Rheumatoid Arthritis. One 1999 study investigated the relationship between hormones, SLE, and rheumatoid arthritis, another autoimmune disease. Higher levels of estrogen are associated with SLE, while lower levels are associated with rheumatoid arthritis. The study found that some patients, in fact, progress from one disease to the other, and that such transitions occur during major hormonal shifts, such as the onset of menopause or pregnancy.

Fibromyalgia. Fibromyalgia, which some experts believe may be another autoimmune disorder, is also a common co-condition in SLE patients.

WHAT ARE THE SYMPTOMS OF SYSTEMIC LUPUS ERYTHEMATOSUS?

SLE symptoms may develop imperceptibly over months or years, or they may appear suddenly. Symptoms tend to be worse during winter months, perhaps because prolonged exposure to sunlight in the summer causes a gradual build-up of factors that trigger symptoms months later.

Arthritic Pain

The most common symptom is joint pain, occurring in about 90% of SLE patients. Characteristics of this symptom vary widely:

- It is often accompanied by swelling and redness.
- It can last from hours to months.

- It may be mild or severe.
- It can occur in one joint, move from one to another, or flare erratically.
- Pain often occurs in the morning and improves during the day, only to return later when the patient tires.
- The joints most affected are fingers, wrists, elbows, knees, and ankles. (Joints in the spine and neck are not affected).

Children may experience these symptoms as growing pains, and, in all patients, they may be the only symptoms for many years.

Fever

Fever occurs in 90% of SLE patients and is usually caused by the inflammatory process of the disease, not by infection. It is low-grade except during an acute lupus crisis.

Skin Rashes

Three-quarters of SLE patients have skin inflammation and skin lesions (ulcers, rashes, or other injured areas). About half of these lesions are photosensitive; that is, they are aggravated by ultraviolet (UV) radiation from sunlight, even from light coming through a window. (UV radiation may even trigger systemic flares in SLE patients.)

A number of different skin conditions have been described in SLE patients.

Discoid Lupus Erythematosus. About 20% of patients have *discoid* lesions. In such cases, the condition is often known as discoid lupus erythematosus (DLE). Patients with this condition may have the following skin abnormalities:

- Discoid means coin-shaped, so these lesions are round and raised. They are also scaly. Untreated, the margins gradually extend outward as the center dries out and atrophies, causing severe scarring. If discoid lesions appear on the scalp, they can plug hair follicles and cause irreversible hair loss. Discoid lesions occasionally appear on the upper portion of the trunk and on the mucous membranes.
- A butterfly-shaped rash across the face may accompany this condition. This rash causes little scarring, although spidery, branching lines of swollen capillaries (the tiniest blood vessels) may appear.

Most patients with this condition have only a limited skin disorder. In only about 10% of cases does discoid lupus develop into full-blown SLE.

Subacute Cutaneous Lupus Erythematosus. Subacute cutaneous lupus erythematosus (SCLE) is characterized by the following:

- Very red, non-scarring, coin-shaped, or psoriasis-like lesions that are acutely photosensitive that usually occur over the arms, neck, and face.
- Joint aches and fatigue (sometimes).

The condition is also often mild and does not affect the central nervous system or kidneys.

Vasculitis. SLE can cause inflammation in the blood vessels (*vasculitis*) that may have the following effects on the skin:

- Red welts may form across large areas of the body.
- Sometimes deep red bumps may appear, particularly on the leg, where they may ulcerate.
- In some people, reddish-purple lesions appear on the pads of fingers and toes or near the nails of fingers and toes.
- Lesions caused by vasculitis may ulcerate or blister if they erupt on mucous membranes in the mouth, nose, or vagina and can be painful if they occur on the throat.

Other Symptoms

Other symptoms include the following:

- Fatigue.
- Loss of appetite, nausea, and weight loss.
- Chest pain.
- Bruising.
- Menstrual irregularities.
- Disturbances of thought and concentration, and personality changes.
- Hair loss (known as *alopecia*) or easy breakage that is not caused by discoid lesions may also occur in about half of SLE patients during severe flares or after pregnancy or severe illness. In such cases, hair grows back.
- SLE patients are two to three times more likely than the general population to suffer migraines.
- Half of SLE patients experience sleep disorders, such as restless legs syndrome and sleep apnea.

HOW SERIOUS IS SYSTEMIC LUPUS ERYTHEMATOSUS?

General Outlook

The only predictable fact about systemic lupus erythematosus is that its course is unpredictable for each individual.

Mild SLE. About 20% to 30% of cases are mild. For many of these patients, the only symptoms may be the skin rashes of discoid lupus erythematosus (DLE) or subacute cutaneous lupus erythematosus (SCLE) with or without joint aches. The number and intensity of symptoms in mild cases often decrease over time, as does the likelihood of major organ involvement. These skin conditions, however, are not absolute insurance

against more severe disease, and patients with mild SLE should be tested for organ involvement.

Widespread SLE. Most commonly, SLE is a chronic, life-long disease, alternating between periods of symptom-relapse, or flares, and remission. The disease may begin in any of the various systems of the body and progress unpredictably to others. The following are typical patterns:

- Symptom relapses, or flares, occur on the average of two or three times a year.
- Between flares, most SLE patients can function at about 90% of normal capacity.

The degree of severity depends on different factors.

- Severity of the inflammatory response.
- Frequency of episodes.
- The degree of organ or system involvement. Vital organs or systems, such as lungs, kidneys, nervous system, joints skin, and others are affected in 50% to 75% of SLE patients. Infections followed by kidney failure are the chief causes of death in SLE patients.

Because of more effective and aggressive treatment, the prognosis for SLE has improved markedly over the past two decades. Long-term progress of the disease is affected greatly by treatment in the initial acute phase of the disease so a speedy and accurate diagnosis is all-important. The ten-year survival rate with treatment is now 85% to 95% and many people have a normal life span. SLE that develops later in life is generally less serious than SLE that strikes in childhood.

Complications of the Blood

Almost 85% of SLE patients experience problems associated with abnormalities in the blood.

Anemia. About half of SLE patients are anemic. Causes include the following:

- The inflammatory process itself, which reduces red-blood cell production.
- Iron deficiencies resulting from excessive menstruation.
- Iron deficiencies from GI bleeding caused by some of the treatments.

The Antiphospholipid Antibody Syndrome. Certain autoantibodies called antiphospholipids are important factors in both anemia and other blood abnormalities in SLE. Of particular interest are two specific ones, *lupus anticoagulant* and *anticardiolipin*, that are highly involved in complex set of blood symptoms known as antiphospholipid antibody syndrome, which include the following:

- *Thrombocytopenia* (low levels of platelets), which impairs clotting, causes bruising and bleeding from the skin, nose, gums, or intestines.

- Other the hand, an *increased* risk for blood clotting caused by the antibody lupus anticoagulant (which means anti-clotting). This poses a higher risk for stroke, heart attack, and spontaneous abortion.
- *Hemolytic anemia* , which prematurely destroys red blood cells. This is caused by the anticardiolipin antibody and occurs in only about 10% of patients. It can be chronic or develop suddenly and severely.

Neutropenia. Commonly, patients with SLE have low counts of white blood cells (a condition called *neutropenia*), but the condition is usually harmless unless the reductions are so severe that they leave the patient vulnerable to infections.

Acute Lupus Hemophagocyte Syndrome. A rare blood complication of SLE that occurs primarily in Asians is called acute lupus hemophagocytic syndrome; it is generally of short duration and characterized by fever and a sudden drop in blood cells and platelets.

Raynaud's Phenomenon

Raynaud's phenomenon is a condition in which cold or stress can cause spasms in impaired blood vessels resulting in pain in fingers and toes. It occurs as part of the inflammatory response in blood vessels, which can narrow them and reduce circulation. In extreme cases, gangrene can result.

Heart and Circulation Complications

Complications involving blood vessels, higher-than normal cholesterol levels (sometimes also from prolonged corticosteroid treatments), and antiphospholipid antibodies have negative effects on many parts of the heart. SLE patients have a higher risk for the following conditions:

- Impaired blood vessel functioning increases the risk for coronary artery disease.
- The risk for and unhealthy cholesterol levels and high blood pressure is higher in patients with SLE, particularly those whose kidney are involved and who have antiphospholipid antibodies.
- The risk for congestive heart failure is higher in SLE women of all ages.
- About 30% of SLE patients experience pericarditis, an inflammation of the tissue surrounding the heart that causes pressure or pain in the chest.
- Inflammation of the heart muscle itself (myocarditis) is uncommon but can lead to irregular heart beats or even heart failure.
- Abnormalities in the valves of the heart occur often in SLE.
- People with SLE are particularly susceptible to the dangers of elevated levels of homocysteine, a chemical that occurs with deficiencies of B6, B12, and folic acid. Homocysteine has been associated with an increased risk for heart attack, strokes, and blood clots (although it may simply be a marker for these conditions).

The risk for blood clots in the heart and brain is much higher than average in younger women with SLE; the risks decline as such women age. In fact, studies report that in

elderly women with SLE the risk for a heart attack or stroke may even be lower than in the general population.

Lung Complications

SLE affects the lungs in about 60% of patients:

- Recurrent inflammation of the membrane lining the lung (*pleurisy*) is the most common problem.
- In some cases, fluid accumulates, a condition called *pleural effusion*, and can cause stabbing localized pain that worsens when coughing, sneezing, laughing, or taking a deep breath.
- Inflammation of the lung itself in SLE is called *lupus pneumonitis*. It can be caused by infections or by the SLE inflammatory process. Symptoms are the same in both cases: fever, chest pain, labored breathing, and coughing. Rarely, lupus pneumonitis becomes chronic and causes scarring in the lungs, which reduces their ability to deliver oxygen to the blood.
- A very serious and also rare condition called *pulmonary hypertension* occurs when high pressure develops in the vessels supplying blood to the lungs.

Kidney Problems (Lupus Nephritis)

The kidneys are a crucial battleground in SLE because it is here that the debris left over from the immune attacks is most likely to be deposited. About 50% of SLE patients exhibit inflammation of the kidneys (called *lupus nephritis*). Kidney abnormalities may affect as many as 75% of African American patients.

Lupus nephritis occurs in different forms and can vary widely in severity.

- *Proliferative nephritis* is a serious variant. It occurs when the inflammatory process causes widespread damage and scarring in the blood vessels of the kidneys, which filters waste products, water, and salts out of the blood. The condition is associated with high blood pressure and kidney deterioration.
- *Membranous lupus nephritis* is another variant that is often associated with a good outlook. In some cases, however, if the kidney is persistently exposed to high protein levels, the disorder can progress to fatal end-stage kidney (renal) disease.

Serious complications occur eventually in about 30% of patients. Being young, African American, and male are particular risk factors for severe kidney problems. Genetic factors appear to influence severity in different individuals. If kidney injury develops, it almost always occurs within 10 years of the onset of SLE, rarely after that.

Central Nervous System Complications

In about half of SLE patients, problems occur in the central nervous system (CNS), which include those in the spinal cord, certain nerves in or leading to the brain, and the

membranes that line the skull cavity. Brain scans and other tests suggest that both the nerves and the insulation around them (myelin) may be damaged.

CNS involvement is more likely to occur in the first year, usually during flare-ups in other organs. Symptoms vary widely and may be indistinguishable from psychiatric or neurologic disorders or from the side effects of some medications used for SLE. They include the following:

- Irritability.
- Emotional disorders (anxiety, depression).
- Mild impairment of concentration and memory.
- Headache. (About 20% of lupus headaches resemble migraines.)
- Occasionally, the reflex systems, sensation, vision, hearing, and motor control can be affected.
- The most serious CNS disorder is inflammation of the blood vessels in the brain, which occurs in 10% of SLE patients. Fever, seizures, psychosis, and even coma can occur.

Central nervous system symptoms are usually transient and mild, although, unfortunately, there is little effective treatment available for them. The severity of CNS symptoms correlates with progression of the disease.

Infections

Infections are a common complication. The immune system is indeed overactive in SLE, but it is also abnormal and reduces the ability to fight infections. Patients are not only prone to the ordinary streptococcal and staphylococcal infections, but they are also susceptible to fungal and parasitic infections (called opportunistic infections), which are common in people with weakened immune systems. They also face an increased risk for herpes, salmonella, and yeast infections. Corticosteroid and immunosuppressants, treatments used for SLE, also increase the risk for infections, thereby compounding the problem.

Gastrointestinal Complications

About 45% of SLE patients suffer gastrointestinal problems, including nausea, weight loss, mild abdominal pain, and diarrhea. Severe inflammation of the intestinal tract occurs in less than 5% of patients and causes acute cramping, vomiting, diarrhea, and, rarely, intestinal perforation, which can be life-threatening. Fluid retention and swelling can cause intestinal obstruction, which is much less serious but causes the same type of severe pain. Inflammation of the pancreas can be caused by the disease and by corticosteroid therapy.

Joint, Muscle, and Bone Complications

Arthritis caused by SLE almost never leads to destruction or deformity of joints. The inflammatory process can, however, damage muscles and cause weakness. SLE patients also commonly experience reductions in bone mass density (osteoporosis) and have a higher risk for fractures, whether or not they are taking corticosteroids (which are known risk factors for osteoporosis).

Eye Complications

Inflamed blood vessels in the eye can reduce blood supply to the retina, resulting in degeneration of nerve cells and a risk of hemorrhage in the retina. The most common symptoms are cotton-wool-like spots on the retina. In about 5% of patients sudden temporary blindness may occur.

Socioeconomic Consequences

In one study, 40% of SLE patients quit work within four years of diagnosis, and many had to modify their work conditions. Significant factors that predicted job loss included high physical demands from the work itself, a more severe condition at the time of diagnosis, and lower educational levels. People with lower income jobs were at particular risk for leaving them.

PREGNANCY AND SYSTEMIC LUPUS ERYTHEMATOSIS

Effect of Pregnancy on SLE Symptoms

In some studies 6% to 15% of women report *fewer* flares during pregnancy. Most flares occur during the first or second trimester and two months after delivery. Women who conceive after at least six months of remission have a lower risk for flares.

Effect of SLE During and After Pregnancy

All lupus pregnancies are regarded as high risk. About 75% of pregnancies are carried to term, although 25% of the babies may be premature.

Miscarriage. About 25% of SLE pregnancies result in miscarriage. The risk for miscarriage is highest in patients with one or more of the following conditions:

- Women who have antiphospholipid antibodies that cause blood clotting problems.
- Women who have active kidney disease.
- Women with hypertension.

Bleeding in Pregnant Woman. There is an increased risk for bleeding problems

after the birth, due to either anti-SLE drugs or SLE itself.

Preeclampsia. Preeclampsia, a dangerous condition associated with high blood pressure that occurs during pregnancy, develops in 20% of pregnant SLE women.

Managing SLE during Pregnancy

Most anti-SLE drugs are safe during pregnancy, although caution is advised with antimalarial and immunosuppressant drugs, and cyclophosphamide should always be avoided. [See also , How Is Systemic Lupus Erythematosus Treated? in this report.]

Antiphospholipid antibodies are usually treated with prednisone, aspirin, or the anticoagulant drug heparin.

One study indicated, however, that *all* pregnant women with SLE should be treated with the blood thinning drug heparin. In the study, when such women were treated with heparin, regardless of whether they had the antibodies, the infant survival rate was 93% compared to only 77% when pregnant women were given heparin only if they tested positive for antiphospholipid antibodies. In some cases life-long treatment may be necessary. For those who have had a miscarriage, one study found that a combination of aspirin and heparin was more protective than aspirin alone in preserving subsequent pregnancies.

Dangers to the Newborn

Thrombocytopenia. During pregnancy anti-phospholipid antibodies may also cross the placenta and cause thrombocytopenia (drop in platelets) in the fetus, although babies with low-platelet counts are nearly always delivered safely.

Neonatal Lupus. Another known risk to the baby is neonatal lupus, which occurs in 3% of SLE pregnancies and usually resolves within 6 months.

Heart Abnormalities. Rarely, a permanent heart abnormality can occur with this condition, but it is treatable.

WHAT TESTS WILL CONFIRM A DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS?

Diagnostic Criteria

In the early stages of the disease, SLE can be difficult to distinguish from other connective tissue disorders, such as rheumatoid arthritis or fibromyalgia, especially if joint pain is a prominent symptom. These autoimmune disorders may also be present as a co-condition. No single test can definitively confirm or rule out SLE and a number are

required before SLE can be diagnosed definitively. [*See Table* , Criteria for Diagnosing System Lupus Erythematosus.]

Criteria for Diagnosing System Lupus Erythematosus
1. Characteristic rash across the cheek
2. Discoid lesion rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Inflammation of membranes in the lungs, the heart, or the abdomen
7. Evidence of kidney disease
8. Evidence of severe neurologic disease
9. Blood disorders, including low red and white blood cell and platelet counts
10. Immunologic abnormalities
11. Positive antinuclear antibody (ANA)
Note: Four of the criteria must be experienced by a patient before a classification of SLE can be made. These criteria, proposed by the American College of Rheumatology, are not to be relied upon solely for diagnosis, however.

Ruling out Other Conditions

The physician should first rule out common conditions that might be causing the symptoms [*see Table*, Conditions Resembling or Accompanying Systemic Lupus Erythematosus]. The physician may, for example, test the synovial fluid (the lubricating liquid surrounding joints) to rule out rheumatoid arthritis. Certain eye and saliva tests may be used if Sjögren's syndrome is suspected.

Some Conditions Resembling or Accompanying Systemic Lupus Erythematosus
Muscle, Joint, and Bone Disease
Scleroderma (hardening of the skin caused by overproduction of collagen).
Multiple sclerosis (fatigue, heaviness or

clumsiness in the arms and legs).
Rheumatoid arthritis (symmetrical joint pain). (Also an autoimmune disease and sometimes occurs with SLE.)
Sjögren's syndrome (characterized by dry eyes and dry mouth).
Mixed connective tissue disorder (very similar to SLE, but milder).
Myositis (inflammation and degeneration of muscle tissues). Fibromyalgia
Skin Diseases
Rosacea (lesions are pus-filled blisters and do not atrophy).
Seborrheic dermatitis (skin lesions on lips and nose).
Lichen planus (affects mucous membranes).
Leukoplakia (affects mucous membranes).
Dermatomyositis (causes bluish-red skin eruptions in face and upper body, accompanied by swelling).
Weber-Christian Disease.

Tests for Autoantibodies

Methods for measuring the antibodies involved with SLE vary and the range of results can be bewildering. Repeat tests may be needed.

Antinuclear Antibodies (ANAs). One test is used to detect antinuclear antibodies (ANA), which attack the cell nucleus.

High levels of ANA are found in more than 98% of SLE patients. A number of other conditions, however, also cause high levels of ANA, so a positive test is not a definite diagnosis for SLE:

- Antinuclear antibodies may be strongly present in other autoimmune diseases (eg, scleroderma, Sjögren's syndrome, or rheumatoid arthritis).
- They also may be weakly present in about 20% to 40% of healthy women.
- Some drugs can also produce positive antibody tests, including hydralazine, procainamide, isoniazid, and chlorpromazine.

A negative ANA test makes a diagnosis of SLE unlikely but not impossible. High or low concentrations of ANA also do not necessarily indicate the severity of the disease, since antibodies tend to come and go in SLE patients.

In general, the ANA test is considered a screening test:

- If SLE symptoms are present and the ANA test is positive, other tests for SLE will be administered.
- If SLE symptoms are not present and the test is positive, the physician will look for other causes, or the results will be ignored if the patient is feeling healthy.

ANA Subtypes. In some cases, physicians may test for specific ANA subtypes.

- Anti-double stranded DNA (Anti-ds DNA) is usually found only in SLE patients. It may play an important role in injury to blood vessels found in SLE and high levels often indicate kidney involvement. Anti-ds DNA levels tend to fluctuate over time and may even disappear.
- Anti-Sm antibodies are also usually found only with SLE. They are more constant and are more likely to be detected in African-American patients.
- When the ANA is negative but the diagnosis is still strongly suspected a test for anti-Ro anti-La antibodies may identify patients with a rare condition called ANA negative, Ro lupus.

Antibodies to SR Proteins. An advance in diagnosing SLE has been the detection of antibodies to molecules called SR proteins, which are carried by most patients. The test accurately detects lupus in 50% to 70% of patients who test positive for these antibodies.

Antiphospholipid Antibodies. In SLE patients in whom blood abnormalities are suspected, tests will be administered to detect the presence of the two major antiphospholipid antibodies:

- The test for the *lupus anticoagulant antibody* measures the time it takes blood to clot. A longer than normal blood clotting time indicates a *higher* chance for clotting in the body and, therefore, the presence of lupus anticoagulant.
- An ELISA test (enzyme-linked immunosorbent assay) is performed to detect the *anticardiolipin antibody*.

As with the ANA, these antibodies also have a tendency to appear and disappear in a single patient.

Miscellaneous Blood Tests

Complement. Blood tests of SLE patients often show low levels of serum complement, a protein in the blood that aids the body's infection fighters. Individual proteins are termed by the letter "C" followed by a number; common complement tests measure C3, C4, C1q, and CH50. There is some evidence that complete deficiencies of C1q may be a key factor

in the inability of the immune system to contain the autoimmunity process. Complement levels are especially low if there is kidney involvement or other disease activity.

LE Cell Tests. The first blood test ever used for SLE called LE (lupus erythematosus) cell test is positive in only about half of patients with SLE and is not used often now.

Blood Count. White and red blood cell and platelet counts are usually lower than normal and depending on severity are used to determine complications, such as anemia or infection.

Skin Tests

If a skin rash is present, the physician may take a biopsy (a tissue sample) from the margin of a skin lesion. A test known as a lupus band detects antibodies known as immunoglobulin G (IgG), which are located just below the outer layer of the tissue sample. They are present in about 80% of patients with active SLE and in between 30% and 40% of those with inactive disease. The biopsy will not differentiate between systemic and discoid lupus, but it can rule out other diseases. Tests for other antibodies will rule out or confirm discoid lupus and subacute cutaneous lupus.

Tests for Serious Complications of SLE

Kidney Damage and Lupus Nephritis. Kidney damage in patients already diagnosed with SLE may be detected from the following tests:

- Blood tests that measure creatinine, a protein metabolized in muscles and excreted in the urine. High levels suggest kidney damage, although it can also be present with normal creative levels.
- Tests for detecting anti-ds DNA antibodies and complement. High levels of anti-ds DNA and low levels of complement C3 suggest kidney damage. (It should be noted, however, that some patients with severe kidney damage show low levels of anti-ds DNA.)
- Urine analyses. They should be performed at four- to six- month intervals to check for signs of kidney involvement.
- A kidney biopsy. This may be performed to determine if lupus nephritis is present when less invasive tests indicate kidney involvement. It is not absolutely accurate but it helps determine treatment. Electron microscopy (very high-powered electronic microscopes) may be especially important in obtaining critical information on the degree of kidney damage.

Lung and Heart Involvement. A chest x-ray may be performed to check lung and heart function. An electrocardiogram and an echocardiogram are administered if heart disease is suspected.

Central Nervous System Complications. SLE occurring in the central nervous system (CNS) can be difficult to diagnose because its symptoms are easily confused with other psychiatric and neurologic conditions.

- Tests of the cerebrospinal fluid (CSF) for elevated levels of autoantibodies are the most reliable ways to detect CNS complications caused by a faulty immune system.
- Additional tests, including electroencephalograms (EEGs), magnetic resonance imaging (MRI), computed tomography (CT), or x-rays may be useful when blood vessel blockage in the brain is suspected.
- If the physician suspects that CNS symptoms are caused by infection, especially for patients who are receiving immunosuppressant therapy, a lumbar puncture should be performed.

Osteoporosis. To detect early osteoporosis in SLE patients whose disease has lasted more than 3.5 years, experts recommend an imaging test called dual energy x-ray absorptiometry (DEXA) to measure bone mineral density.

WHAT ARE THE GENERAL GUIDELINES FOR TREATING SYSTEMIC LUPUS ERYTHEMATOSUS?

No treatment cures systemic lupus erythematosus, but many therapies can suppress symptoms and relieve discomfort. Treatment of SLE varies depending on the extent and severity of the disease.

Treating Mild Systemic Lupus Erythematosus

Less intensive treatments may be effective for symptoms of mild lupus. They include the following:

- Creams and sunblocks for rashes.
- Nonsteroidal anti-inflammatory drugs for fever, arthritis, and headache.
- Antimalarial agents are more intensive drugs but may be useful for pleurisy, mild kidney involvement, and inflammation of the tissue surrounding the heart.

[See What Are Agents Used for Mild Systemic Lupus Erythematosus?]

Treating Severe Systemic Lupus Erythematosus

More aggressive treatment is needed if there is serious disease progression, evidenced by the following:

- Hemolytic anemia.
- Low platelet count with an accompanying rash (thrombocytopenic purpura).
- Major involvement in the lungs or heart.

- Significant kidney damage.
- Acute inflammation of the small blood vessels in the extremities or gastrointestinal tract.
- Severe central nervous system symptoms.

The primary approach to treating severe SLE is to suppress the immune factors, most often first with corticosteroids and other immunosuppressant agents. Investigative agents and procedures are also showing promise. [*See What Are Specific Agents Used for Severe Systemic Lupus Erythematosus?*]

Treating Specific Complications

The major complications of the disease must be treated as separate problems, keeping in mind the specific aspects of SLE. They are discussed in another section. [*See What Are Treatments for Some Complications of Systemic Lupus Erythematosus?.*]

WHAT ARE AGENTS USED FOR CUTANEOUS AND MILD LUPUS ERYTHEMATOSUS?

Treatment of Skin Problems

Creams. Steroid creams are often used for skin lesions, although many patients with discoid lupus do not respond to steroids, particularly eruptions that are caused by sun sensitivity. A cream derived from vitamin A (Tegison) has been beneficial for some lesions that do not clear up with steroid creams.

Sun Protection. Sun protection is essential. Patients should always use sunblock creams (not just sunscreens) and always wear hats and clothing made of tightly woven fabrics.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Common NSAIDs. The most common pain-relievers for SLE are the nonsteroidal anti-inflammatory drugs (NSAIDs). These agents block prostaglandins, the substances that dilate blood vessels and cause inflammation and pain. There are dozens of NSAIDs. Some of the most common are aspirin, ibuprofen, naproxen, and ketoprofen, but many others are now available.

Timing of Administration. Studies have indicated that the optimal time for taking an NSAID might be after the evening meal and then again on awakening. The reason for this is RA symptoms increase gradually during the night, reaching their greatest severity at the time of awakening. Taking NSAIDs with food can reduce stomach discomfort, although it may slow down the pain-relieving effect.

Side Effects and Complications. Regular use of even over-the-counter NSAIDs may be hazardous for anyone and has been associated with the following side effects:

- Ulcers and gastrointestinal bleeding. This is the major danger with long-term use of NSAIDs. [*See Box Ulcers and Gastrointestinal Bleeding.*]
- Increased blood pressure. This is a particular problem in those on medications to reduce hypertension. Piroxicam (Feldene), naproxen (Aleve), and indomethacin (Indocin) appear to pose the greatest risks for high blood pressure. (Sulindac has the smallest effect.) People with hypertension, severe vascular disease, kidney or liver problems, and those taking diuretics must be closely monitored if they need to take NSAIDs.
- May delay the emptying of the stomach, which could interfere with the actions of other SLE drugs. The elderly are at special risk.
- Dizziness, ringing in the ear.
- Headache.
- Skin rash.
- Depression has also been noted.
- Confusion or bizarre sensation (in some higher-potency NSAIDs, such as indomethacin).
- Kidney abnormalities have been reported in people taking NSAIDs, which resolves when the drugs are withdrawn. Any sudden weight gain or swelling should be reported to a physician.
- Diabetics taking oral hypoglycemics may need to adjust the dosage if they also need to take NSAIDs because of possible harmful interactions between the drugs.

Note. Pain-killers that do *not* reduce inflammation, such as acetaminophen (eg, Tylenol) or opioids (such as codeine), may actually produce additional damage. If pain is suppressed but inflammation is not, joint use can exacerbate the inflammation and release more destructive enzymes.

Ulcers and Gastrointestinal Bleeding

NSAIDs are a major cause of ulcers and gastrointestinal (GI) bleeding. Gastrointestinal complications from the use of NSAIDs account for almost 100,000 hospitalizations and at least 16,000 deaths a year in the United States. Bleeding and ulcers can occur at any time, with or without symptoms. One study indicated that taking NSAIDs for only six months posed a risk for symptomatic ulcers that was greater than 1%. The risk for bleeding is continuous as long as a patient is on these drugs and may even persist as long as a year after the drug is discontinued. Alcohol abuse may increase the risks for GI bleeding when taking NSAIDs. Because NSAIDs reduce the clotting of the blood, anyone undergoing surgery should stop taking the medication a week before the operation.

Ulcer Risk for Specific NSAIDs. One study ranked the sixteen most commonly used NSAIDs according to risk for ulcers and bleeding.

- Lowest Risk: nabumetone (Relafen), etodolac (Lodine), salsalate, and sulindac (Clinoril).
- Medium risk: diclofenac (Voltaren), ibuprofen (Motrin, Advil, Nuprin, Rufen), aspirin, naproxen (Aleve, Naprosyn, Naprelan, Anaprox), and tolmetin (Tolectin). (Drugs within this group vary in risk. Studies show,

for example, that short-term use of naproxen is twice as likely as ibuprofen to be associated with hospitalization from GI bleeding. Although ketoprofen (Actron, Orudis KT) was considered a medium-risk drug, another study reported that even one week of taking the drug at low doses causes significant GI injury.

Highest risk: flurbiprofen (Ansaid), piroxicam (Feldene), fenoprofen, indomethacin (Indocin), meclofenamate (Meclomen), and oxaprozin.

Drugs for Prevention of NSAID-Induced Ulcers. For people who need to take NSAIDs regularly, some agents are available that may protect against bleeding and ulcers.

- Proton-pump inhibitors include omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), and pantoprazole. Proton pump inhibitors are possibly the most protective agents and can actually heal existing ulcers. Their use has been demonstrated to reduce NSAID-ulcer rates by as much as 80% compared with no treatment.
- *Misoprostol.* Misoprostol is a prostaglandin, the protective substance blocked by NSAID use. It protects against the major intestinal toxicity of NSAIDs. It is used to prevent NSAID-induced ulcers, both duodenal and gastric, but is not useful in healing existing ulcers.
- *H2 Blockers.* Some H2 blockers may help prevent NSAID-induced ulcers. These drugs are available over the counter and include famotidine (Pepcid AC), ranitidine (Zantac), cimetidine (Tagamet), and nizatidine (Axid). In one 2000 study, ranitidine and famotidine were associated with a lower risk for bleeding in patients taking NSAIDs, but another study found no protection from cimetidine.

COX-2 Inhibitors

Celecoxib (Celebrex), rofecoxib (Vioxx), and meloxicam (Mobic) are known as COX-2 (cyclooxygenase-2) inhibitors, the so-called super-aspirins. These agents may prove to be as effective and less harmful to the GI tract than NSAIDs. Theoretically, they may even have properties that produce less adverse effects on cartilage than NSAIDs may have. They may be effective for gout, although there is no data on the use of these agents for gout patients as yet.

Some studies have found that patients taking COX-2 inhibitors have the same gastrointestinal *symptoms* (eg, diarrhea, abdominal discomfort) as standard NSAIDs. (Other side effects found with short-term use include headache and dizziness.) Importantly, however two 2000 studies reported a lower incidence of ulcers and other toxic side effects in patients taking the COX-2 inhibitors than in those taking NSAIDs. The drugs were all equally effective in relieving pain. (One study compared celecoxib with the NSAIDs ibuprofen or diclofenac and the other compared rofecoxib with the NSAID naproxen). One 1999 study even found the rate of GI problems with celecoxib was equal to that in people who do not take NSAIDs at all. COX-2 inhibitors are currently more expensive than traditional NSAIDs, however, and some insurers do not pay for them.

Possible Negative Effects. In spite of their promise, some researchers theorize that inhibiting COX-2 may have some negative side effects over the long term:

- One 2000 study observed that the COX-2 inhibitors had some adverse effects on kidney function, particularly in elderly people, that were similar to the effects of standard NSAIDs.
- Patients taking anticoagulant drugs may experience a higher risk for bleeding with the use of these agents.
- The use of COX-2 inhibitors can also increase the blood levels of many other drugs taken concurrently, including warfarin, ACE inhibitors, and methotrexate.
- A few cases of psychiatric side effects (hallucinations), fluid build up, high blood pressure, and excess potassium in the blood has been observed with higher doses of celecoxib or rofecoxib.
- They may have negative effects on pregnancy and fertility.

More research is needed to confirm or refute any possible hazard.

Other Investigative Alternatives to NSAIDs

NO-NSAIDS. Experimental agents are being developed that combine nitric oxide with NSAIDs (NO-NSAIDs). Nitric oxide increases blood flow in the mucous lining and secretions of mucus and bicarbonate. Combining nitric oxide with NSAIDs may provide benefits similar to the COX-2 inhibitors.

Antimalarial Drugs

Antimalarial drugs may be prescribed for if discoid lupus or other skin problems and joint pains are the predominant symptoms:

- The most common antimalarial agent used is **hydroxychloroquine** (Plaquenil). **Hydroxychloroquine** is effective as maintenance therapy to reduce flares in patients with mild or inactive disease.
- Others include chloroquine (Aralen) or quinacrine (Atabrine).

It is not known why these drugs work; some researchers believe they inhibit the immune response and others think they interfere specifically with inflammation.

Hydroxychloroquine may reduce the risk of blood clots as well as reduce cholesterol levels that have been increased in those taking corticosteroids.

High doses may be prescribed initially in order to accumulate high levels of the drug in the blood stream.

Side Effects. Side effects of the antimalarials include the following:

- Skin rash.
- Change in skin color (yellow in the case of quinacrine).

- Gastrointestinal problems.
- Headache.
- Hair loss.
- Muscle aches.
- The most serious is damage to the retina, although this is very uncommon when low doses are used. Eye damage after taking **hydroxychloroquine** is reversible when caught in time and treated, but it is not reversible if it develops after taking chloroquine. An eye exam is advisable every six months or so.

Antimalarials may also be used in combination with other anti-SLE drugs, including immunosuppressants and corticosteroids. [*see below*]. It should be noted that smoking significantly reduces the effectiveness of antimalarial drugs.

Experimental Agents for Cutaneous Lupus

Thalidomide. Thalidomide inhibits a number of potent cytokines and reduces the formation of new blood vessels that allow the disease to progress. Although it is notorious for causing birth defects, it is now being investigated for many autoimmune diseases. In low doses it may be safe and effective for severe cutaneous lupus. It does not appear to have any benefits for systemic complications of lupus.

WHAT ARE SPECIFIC AGENTS USED FOR SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS?

Corticosteroids

Severe SLE is treated with corticosteroids, also called steroids, which suppress the inflammatory process, and help relieve many of the complications and symptoms, including anemia and kidney involvement. Oral prednisone (Deltasone, Orasone) is usually prescribed. Other agents include methylprednisolone (Medrol, Solumedrol), hydrocortisone, and dexamethasone (Decadron).

Some people need to take oral prednisone for only a short time; others may require it for long durations. An intravenous administration of methylprednisolone using "pulse" therapy for three days is proving useful for flare-ups in the joints. Combinations with other drugs, particularly immunosuppressants, may be beneficial.

Regimens vary widely depending on the severity and location of the disease. Most SLE patients can eventually function without prednisone, although some may have to choose between the long-term toxicity of corticosteroids and the complications of active disease.

Side Effects of Long-Term Oral Corticosteroids. Unfortunately, serious and even life-threatening complications have been associated with long-term steroid use. Adverse effects of prolonged use of oral steroids include cataracts, glaucoma, osteoporosis, diabetes, fluid retention, susceptibility to infections, weight gain, hypertension, capillary

fragility, acne, excess hair growth, wasting of the muscles, menstrual irregularities, irritability, insomnia, and psychosis. Osteoporosis is a common and particularly severe long-term side effect of prolonged steroid use. Medications that can prevent osteoporosis include calcium supplements, parathyroid hormone, alendronate etidronate, risedronate, or hormone replacement therapy in post-menopausal women. Vitamin C and E may help reduce the risk of cataracts.

Withdrawal from Long-Term Use of Oral Corticosteroids. Long-term use of oral steroid medications suppresses secretion of natural steroid hormones by the adrenal glands. After withdrawal from these drugs, this so-called adrenal suppression persists and it can take the body a while (sometimes up to a year) to regain its ability to produce natural steroids again. It should be noted that there have been a few cases of severe adrenal insufficiency that occurred when switching from oral to inhaled steroids, which, in rare cases, has resulted in death.

No one should stop taking any steroids without consulting a physician first, and if steroids are withdrawn, regular follow-up monitoring is necessary. Patients should discuss with their physician measures for preventing adrenal insufficiency during withdrawal, particularly during stressful times, when the risk increases.

Immunosuppressant Drugs

Drugs known as immunosuppressants are often used, either alone or with corticosteroids for very active SLE, particularly when kidney or neurologic involvement or acute blood vessel inflammation is present. These drugs suppress the immune system by damaging cells that grow rapidly, including those that produce antibodies. About a third of patients take immunosuppressants at some point in the course of the disease.

Types of Immunosuppressants. The most common immunosuppressants are the following:

- Azathioprine (Imuran). Azathioprine has the lowest toxicity but is also less effective than others.
- Methotrexate (Rheumatrex). One study indicated that patients with even mild SLE who take methotrexate experience improved symptoms, less pain, and lower steroid requirements.
- Cyclophosphamide (Cytosan).

Mycophenolate mofetil is a promising new immunosuppressant showing particularly effectiveness for complications in the kidney. Other drugs commonly used include chlorambucil (Leukeran), nitrogen mustard (Mustargen), and cyclosporine (Sandimmune).

One center reported that the use of these drugs reduced disease activity by 33%. Combining them with corticosteroids may allow the steroid to be withdrawn more quickly.

General Side Effects. The most frequent side effects of immunosuppressants are stomach and intestinal distress, skin rash, and mouth sores. Hair loss can occur. Over-suppression of the immune system can cause low blood cell counts and serious side effects, including anemia, menstrual irregularity, possible ovarian failure and permanent infertility, herpes zoster (shingles), liver and bladder toxicity, and an increased risk of cancer. Sterility in female patients may be averted by administering pulsed doses at the time of menstruation. In general, immunosuppressants should not be used alone unless corticosteroids are ineffective or inappropriate. Grapefruit juice has an enzyme that may enhance the effects of some immunosuppressants.

Dehydroepiandrosterone (DHEA)

SLE patients have very low levels of dehydroepiandrosterone (DHEA). This is a mild male hormone that is produced in the fetus, production stops at birth, and then resumes at age 7. DHEA is converted into testosterone and estrogen. Production peaks at 30 and then declines slowly throughout the remaining years.

Studies from 1999 and 2000 suggest that treatment agents derived from DHEA, called GL701 or prasterone (Aslera), reduce flares by between 26% and 46%. DHEA may also offer additional benefits, particularly in helping to prevent loss of bone density in patients taking steroids. Because of the relationship between estrogen and SLE, researchers are also investigating the use of male hormones, such as danazol (Danocrine). Side effects of DHEA and male hormones include acne and hair growth.

Blood Exchange Procedures

Plasmapheresis. Plasmapheresis is a process in which the fluid part of the blood, called plasma, is removed from blood cells:

- The patient lies in a reclining chair and two thin tubes are placed in veins on an arm on one side and usually a hand on the other (so it can be mobile). The discomfort is the same as experience when giving blood. The procedure takes a few hours, however.
- The blood is withdrawn from one arm and undergoes cell separation. This may be done using a centrifuge (a device that spins the blood so that the heavier particles drop to the bottom) or using a membrane with very small holes.
- The blood cells are returned through the other arm, while the plasma, which contains inflammatory antibodies and other immunologically active substances, is discarded and replaced with other fluids, which are also then replaced.
- Medication to keep the blood from clotting (an anticoagulant) is given during the procedure.

Plasmapheresis is not useful for routine management of patients but may have some benefits in specific cases, such as lupus patients with hemolytic anemia.

Photopheresis. Photopheresis is a promising variant. Prior to blood removal, the patient receives methoxypsoralen (either in oral or injected form), which is a chemical that acts with ultraviolet (UVA) light to change the DNA of the blood cells. The blood is removed and specific white blood cells are treated with UVA light prior to reinfusion. The targeted cells are those involved with lupus. After treatment they are unable to replicate and are eliminated from the body. Multiple case reports suggest that this therapy can benefit SLE patients with mild to moderate disease, but further study is needed.

Experimental Treatments

A number of genetically designed drugs are being developed to target harmful immune factors without damaging other parts of the immune system.

Monoclonal Antibodies. A number of genetically designed antibodies, called monoclonal antibodies, are being investigated that target specific factors in the immune system believed to be important in the disease process. One, for example, blocks complement (immune factors critical for disease in the kidney). A small 2000 study used a monoclonal antibody to target the potent immune factor interleukin-10 (IL-10). All the patients improved significantly both during the treatment and for 2 months afterwards, and remained stable through six months of follow-up.

Vaccines. Other investigative therapies are vaccines used to boost the patient's own immune system. One vaccine for instance is used against double stranded DNA (dsDNA) antibodies, which are important in the SLE disease process.

Intravenous Gamma Globulin. Intravenous gamma globulin has been beneficial against antiphospholipid antibodies, and has shown promise in some studies.

Stem Cell Transplantation. Some patients with severe SLE have achieved at least short term remission after undergoing transplantation of hematopoietic stem-cells, which are immature blood cells that develop into red and white blood cells and platelets. In one very small US study of patients with severe SLE, high dose chemotherapy combined with stem-cell transplantation was extremely effective. All the patients who underwent successful transplantation experienced remission of SLE for 25 months. Their T-cell levels normalized, their anti-nuclear and anti-ds DNA antibody levels dropped to normal, complement levels normalized, and the function of their internal organs improved significantly. The procedure is experimental, however, and has some serious risks.

TREATMENTS FOR SOME COMPLICATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS	
Infections or Inflammation in the Lungs	<i>Preventive Measures.</i> Immunizations with inactive viruses and preventive antibiotics should be considered for SLE patients at high risk for infection. <i>Treating Infections.</i> When they occur infections need to be

	<p>treated aggressively with antibiotics. (Note: Antibiotic drugs such as penicillin or the sulfa drugs may cause sensitivity rashes that can be confused with SLE rash.)</p> <p><i>Treating Lung Inflammation.</i> It should be noted that inflammation of the lung (pneumonitis) resembles pneumonia but is not an infection but is a result of the autoimmune process. This condition needs to be treated with corticosteroids or immunosuppressants, but only if the physician is sure infection is not present.</p>
<p>Bleeding and Clotting Disorders</p>	<p><i>Excess Bleeding.</i> Surgical removal of the spleen may be advisable if bleeding disorders are a serious problem, but this option should be considered carefully, because the spleen provides one line of defense against infection. (Abnormal spleen function, in any case, appears to be fairly common in SLE.)</p> <p><i>Clotting Disorders.</i> If a patient is believed to be at risk for blood clots because of the presence of the antiphospholipid antibodies, treatment with anticoagulants such as aspirin, warfarin (Coumadin), or heparin is advisable.</p>
<p>Kidney Disease</p>	<p><i>Drugs</i></p> <p>_ Steroids are the most effective and rapid drugs for treating active kidney disease and for managing milder forms of nephritis. They also might be useful for initial treatment of proliferative nephritis in some cases, particularly women who want to become pregnant, although this is under debate.</p> <p>_ Cyclophosphamide at this time is the most effective drug for proliferative lupus nephritis, and, in combination with a steroid, has been shown to control proliferative nephritis in between 60% and 90% of patients. Because of its effect on fertility, however, some physicians prefer avoiding cyclophosphamide and use a steroid alone as long as possible. Others are concerned however, that delaying cyclophosphamide in severe nephritis can cause permanent kidney scarring.</p> <p>_ Small studies indicate that mycophenolate mofetil (commonly used during organ transplantation to prevent tissue rejection) may also be effective in treating kidney disease associated with SLE.</p> <p><i>Procedures</i></p> <p>Kidney transplant or dialysis should be considered for SLE patients with severe kidney damage. For unknown reasons, SLE does not generally recur in the transplanted kidneys. Studies are conflicting, however, over whether SLE transplant patients have higher organ-rejection rates than other kidney-transplant recipients. Both transplantation and dialysis have potentially serious complications.</p> <p><i>Plasmapheresis</i></p> <p>Whether plasmapheresis is beneficial for SLE kidney disease is not yet clear.</p>
<p>Osteoporosis</p>	<p>Treatments for osteoporosis include calcium, vitamin D, bisphosphonates, parathyroid hormone, and newer so-called Selective estrogen-receptor modulators (SERM). SERMs, such as tamoxifen (Nolvadex), raloxifene (Evista),</p>

	<p>and tibolone (Livial), are of particular interest in SLE because they have been designed to produce the benefits of estrogen without some of its adverse effects, such as hormone-related breast cancer. Animal studies suggest that they may even have some protective effects on the SLE disease process itself, although one study reported no benefits on SLE patients, and some patients even deteriorated.</p> <p>(Hormone replacement therapy, which is traditionally used to protect bone loss in postmenopausal women, is probably not appropriate for SLE patients.)</p>
<p>Heart Disease</p>	<p>The need for aggressive treatment of high blood pressure often accompanies kidney disease. SLE is also accompanied by high cholesterol levels, which also require diet and usually drug therapies. [See <i>High Blood Pressure, Comprehensive Version, Cholesterol, Other Lipids, and Lipoproteins</i>, and <i>Diet, Heart-Healthy</i>.]</p>

WHAT ARE LIFESTYLE MEASURES FOR MANAGING SYSTEMIC LUPUS ERYTHEMATOSUS?

Dietary Recommendations

The following are some tips for maintaining a healthy diet:

- Cultivating a diet low in saturated fats. Not all fats are unhealthy however. Some studies suggest that omega-3 fatty acids, which are fat compounds found in fish oil, black currant or primrose seed oils, and flax seed, have anti-inflammatory and nerve protecting actions.
- Choose whole grains and fresh vegetables and fruits. According to some studies, a diet rich in fruits and vegetables can lower homocysteine levels, which are elevated in SLE patients and may be a risk factor for heart disease. Researchers are also investigating compounds called indoles, also known as mustard oil, which are found in broccoli, cabbage, Brussels sprouts, cauliflower, kale, kohlrabi, collard and mustard greens, rutabaga, turnips, and bok choy. Indoles stimulate enzymes that convert estrogen to a more benign type. Eating vegetables certainly will not cure SLE, but they offer many health benefits in general.
- Obtaining most proteins from vegetables, particularly soy, and avoiding dairy and meat products may help protect the kidneys.
- Patients should take extra calcium and vitamin D, particularly if they are on corticosteroids.
- Supplements of vitamins B12, B6, and folate may be necessary, especially in people whose blood tests show high levels of homocysteine.

- Exercise is safe, but patients should not expect it to improve symptoms, including joint aches and fatigue.
- Patients should restrict salt, particularly if they have signs of hypertension and kidney disease.

Prevention against Infections

Patients should minimize their exposure to crowds or people with contagious illnesses. Careful hygiene, including dental hygiene, is also important.

Avoiding SLE Triggers


Simple preventative measures include avoiding overexposure to ultraviolet rays and wearing protective clothing and sunblocks. There is some concern that allergy shots may cause flare ups in certain cases. Patients who may benefit from them should discuss risks and benefits with an SLE specialist. In general, SLE patients should use only hypoallergenic cosmetics or hair products.


Reducing Stress


Chronic stress has profound physical effects and influences the progression of SLE. According to one 1999 study, SLE patients differ from healthy individuals in their immune responses to stress, and psychological stress can induce flare-ups in SLE patients. Patients should try to avoid undue emotional or physical stress. Getting adequate rest of at least 8 hours and possibly a nap during the day may be helpful. Maintaining social relationships and healthy activities helps prevent the depression and anxiety associated with the disease.

WHERE ELSE CAN HELP BE FOUND FOR SYSTEMIC LUPUS ERYTHEMATOSUS?

Lupus Foundation of America, Inc., 1300 Piccard Drive, Suite 200, Rockville, MD 20850-4303.

Call (301-670-9292) or call (800-558-0121) or on the Internet (<http://www.lupus.org/>)
The foundation is an excellent organization with good support groups and information.

National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson Street, Denver, CO 80206. Call (800-222-LUNG or 303-355-LUNG) or on the Internet (<http://www.njc.org/>)
This excellent organization publishes a number of booklets for the public and offers an information line staffed by trained nurses.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), One AMS Circle, Bethesda MD 20892-3675. Call (301-495-4484) or on the Internet (<http://www.nih.gov/niams/>)

The institute provides an information packet and two bibliographies of resources, one for health professionals and one for osteoarthritis patients.

The Arthritis Foundation, 1314 Spring St NW, Atlanta GA 30309. Call (800-283-7800) or on the Internet (<http://www.arthritis.org>)

The Arthritis Foundation has 73 local chapters in metropolitan areas. This foundation provides information about SLE as well as the treatment of arthritis.

American Autoimmune Related Diseases Association, Inc., 22100 Gratiot Ave., Detroit, MI 48021-205. Call (810-776-3900) or on the Internet (<http://www.aarda.org>)

Alliance of Genetic Support Groups, 4301 Connecticut Avenue, NW, Suite 404, Washington, DC 20008-2304. Call (800-336-GENE) or (202-966-5557) or on the Internet (<http://www.geneticalliance.org>)

SLE Foundation of America, 149 Madison Avenue, New York, NY 10016. On the Internet, (<http://www.lupusny.org>).

American College of Rheumatology, 1800 Century Place, Suite 250, Atlanta, GA 30345. Call 404-633-3777 or on the Internet (<http://www.rheumatology.org>)

Lists local and international SLE organizations

(<http://www.hamline.edu/lupus/addresses.html>)

Good in-depth information (<http://cerebel.com/lupus>)

Canadian organization (<http://www.lupuscanada.org>) or call (403-274-5599).

Valdecoxib (003541)

CATEGORIES:

Indications: Arthritis, osteoarthritis; Arthritis, rheumatoid; Dysmenorrhea, primary

Pregnancy Category C

FDA Approved 2001 Nov

DRUG CLASS: Analgesics, non-narcotic; COX-2 inhibitors; Nonsteroidal anti-inflammatory drugs

BRAND NAMES: **Bextra** (US);

DESCRIPTION:

Valdecoxib is chemically designated as 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide and is a diaryl substituted isoxazole.

The empirical formula for valdecoxib is C₁₆H₁₄N₂O₃S, and the molecular weight is 314.36. Valdecoxib is a white crystalline powder that is relatively insoluble in water (10 µg/ml) at 25°C and pH 7.0, soluble in methanol and ethanol, and freely soluble in organic solvents and alkaline (pH=12) aqueous solutions.

Bextra tablets for oral administration contain either 10 or 20 mg of valdecoxib. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

CLINICAL PHARMACOLOGY:

Mechanism of Action

Valdecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties in animal models. The mechanism of action is believed to be due to inhibition of prostaglandin synthesis primarily through inhibition of cyclooxygenase-2 (COX-2). At therapeutic plasma concentrations in humans valdecoxib does not inhibit cyclooxygenase-1 (COX-1).

Pharmacokinetics

Absorption

Valdecoxib achieves maximal plasma concentrations in approximately 3 hours. The absolute bioavailability of valdecoxib is 83% following oral administration of valdecoxib compared to intravenous infusion of valdecoxib.

Dose proportionality was demonstrated after single doses (1-400 mg) of valdecoxib. With multiple doses (up to 100 mg/day for 14 days), valdecoxib exposure as measured by the AUC, increases in a more than proportional manner at doses above 10 mg bid. Steady state plasma concentrations of valdecoxib are achieved by day 4.

The steady state pharmacokinetic parameters of valdecoxib in healthy male subjects are shown in [TABLE 1](#).

TABLE 1 Mean (SD) Steady State Pharmacokinetic Parameters After Valdecoxib 10 mg Once Daily for 14 Days	
	Healthy Male Subjects
Pharmacokinetic Parameter	(n=8, 20-42 years)

TABLE 1 Mean (SD) Steady State Pharmacokinetic Parameters After Valdecoxib 10 mg Once Daily for 14 Days

	Healthy Male Subjects
Pharmacokinetic Parameter	(n=8, 20-42 years)
AUC(0-24h) (h·ng/ml)	1479.0 (291.9)
C _{max} (ng/ml)	161.1 (48.1)
T _{max} (h)	2.25 (0.71)
C _{min} (ng/ml)	21.9 (7.68)
Terminal half-life (h)	8.11 (1.32)

No clinically significant age or gender differences were seen in pharmacokinetic parameters that would require dosage adjustments.

Effect of Food and Antacid

Valdecoxib can be taken with or without food. Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of valdecoxib when valdecoxib was taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1-2 hours. Administration of valdecoxib with antacid (aluminum/magnesium hydroxide) had no significant effect on either the rate or extent of absorption of valdecoxib.

Distribution

Plasma protein binding for valdecoxib is about 98% over the concentration range (21-2384 ng/ml). Steady state apparent volume of distribution (V_{ss}/F) of valdecoxib is approximately 86 L after oral administration. Valdecoxib and its active metabolite preferentially partition into erythrocytes with a blood to plasma concentration ratio of about 2.5:1. This ratio remains approximately constant with time and therapeutic blood concentrations.

Metabolism

In humans, valdecoxib undergoes extensive hepatic metabolism involving both P450 isoenzymes (3A4 and 2C9) and non-P450 dependent pathways (*i.e.*, glucuronidation). Concomitant administration of valdecoxib with known CYP 3A4 and 2C9 inhibitors (*e.g.*, fluconazole and ketoconazole) can result in increased plasma exposure of valdecoxib (see [DRUG INTERACTIONS](#)).

One active metabolite of valdecoxib has been identified in human plasma at approximately 10% the concentration of valdecoxib. This metabolite, which is a less potent COX-2 specific inhibitor than the parent, also undergoes extensive metabolism and constitutes less than 2% of the valdecoxib dose excreted in the urine and feces. Due to its low concentration in the systemic circulation, it is not likely to contribute significantly to the efficacy profile of valdecoxib.

Excretion

Valdecoxib is eliminated predominantly via hepatic metabolism with less than 5% of the dose excreted unchanged in the urine and feces. About 70% of the dose is excreted in the urine as metabolites, and about 20% as valdecoxib N-glucuronide. The apparent oral clearance (CL/F) of valdecoxib is about 6 L/h. The elimination half-life ($T_{1/2}$) is approximately 8-11 hours.

Special Populations

Geriatric

In elderly subjects (>65 years), weight-adjusted steady state plasma concentrations [AUC(0-12h)] are about 30% higher than in young subjects. No dose adjustment is needed based on age.

Pediatric

Valdecoxib has not been investigated in pediatric patients below 18 years of age.

Race

Pharmacokinetic differences due to race have not been identified in clinical and pharmacokinetic studies conducted to date.

Hepatic Insufficiency

Valdecoxib plasma concentrations are significantly increased (130%) in patients with moderate (Child-Pugh Class B) hepatic impairment. In clinical trials, doses of valdecoxib above those recommended have been associated with fluid retention. Hence, treatment with valdecoxib should be initiated with caution in patients with mild to moderate hepatic impairment and fluid retention. The use of valdecoxib in patients with severe hepatic impairment (Child-Pugh Class C) is not recommended.

Renal Insufficiency

The pharmacokinetics of valdecoxib have been studied in patients with varying degrees of renal impairment. Because renal elimination of valdecoxib is not important to its disposition, no clinically significant changes in valdecoxib clearance were found even in patients with severe renal impairment or in patients undergoing renal dialysis. In patients undergoing hemodialysis the plasma clearance (CL/F) of valdecoxib was similar to the CL/F found in healthy elderly subjects (CL/F about 6-7 L/h) with normal renal function (based on creatinine clearance).

NSAIDs have been associated with worsening renal function and use in advanced renal disease is not recommended (see [PRECAUTIONS, Renal Effects](#)).

Drug Interactions

Also see [DRUG INTERACTIONS](#).

General

Valdecoxib undergoes both P450 (CYP) dependent and non-P450 dependent (glucuronidation) metabolism. *In vitro* studies indicate that valdecoxib is not a significant inhibitor of CYP 1A2, 3A4, or 2D6 and is only a weak inhibitor of CYP 2C9 and 2C19 at therapeutic concentrations. The P450-mediated metabolic pathway of valdecoxib predominantly involves the 3A4 and 2C9 isozymes. Using prototype inhibitors and substrates of these isozymes, the following results were obtained. Coadministration of a known inhibitor of CYP 2C9/3A4 (fluconazole) and a CYP 3A4 (ketoconazole) inhibitor enhanced the total plasma exposure (AUC) of valdecoxib. Coadministration of valdecoxib with warfarin caused a small, but statistically significant increase in plasma exposures of R-warfarin and S-warfarin, and also in the pharmacodynamic effects (International Normalized Ratio-INR) of warfarin. (See [DRUG INTERACTIONS](#).)

Coadministration of valdecoxib, or its injectable prodrug, with substrates of CYP 2C9 (propofol) and CYP 3A4 (midazolam, alfentanil, fentanyl) did not inhibit the metabolism of either substrate.

Coadministration of valdecoxib with a CYP 3A4 substrate (glyburide) or a CYP 2D6 substrate (dextromethorphan) did not result in clinically important inhibition in the metabolism of these agents.

CLINICAL STUDIES:

The efficacy and clinical utility of valdecoxib tablets have been demonstrated in osteoarthritis (OA), rheumatoid arthritis (RA) and in the treatment of primary dysmenorrhea.

Osteoarthritis

Valdecoxib was evaluated for treatment of the signs and symptoms of osteoarthritis of the knee or hip, in five double-blind, randomized, controlled trials in which 3918 patients were treated for 3-6 months. Valdecoxib was shown to be superior to placebo in improvement in three domains of OA symptoms: (1) the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness and functional measures in OA, (2) the overall patient assessment of pain, and (3) the overall patient global assessment. The two 3 month pivotal trials in OA generally showed changes statistically significantly different from placebo, and comparable to the naproxen control, in measures of these domains for the 10 mg/day dose. No additional benefit was seen with a valdecoxib 20 mg daily dose.

Rheumatoid Arthritis

Valdecoxib demonstrated significant reduction compared to placebo in the signs and symptoms of RA, as measured by the ACR (American College of Rheumatology) 20 improvement, a composite defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in 3 of the following 5: patient global, physician global, patient pain, patient function assessment, and the erythrocyte sedimentation rate (ESR). Valdecoxib was evaluated for treatment of the signs and symptoms of rheumatoid arthritis in four double-blind, randomized, controlled studies in which 3444 patients were treated for 3-6 months. The two 3 month pivotal trials compared valdecoxib to naproxen and placebo. The results for the ACR20 responses in these trials are shown in [TABLE 2](#). Trials of valdecoxib in rheumatoid arthritis allowed concomitant use of corticosteroids and/or disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, gold salts, and hydroxychloroquine. No additional benefit was seen with a valdecoxib 20 mg daily dose.

TABLE 2 ACR20 Response Rate (%) in Rheumatoid Arthritis		
	Study 1	Study 2
Valdecoxib 10 mg/day	49% [†] (103/209)	46% [†] (106/226)
Valdecoxib 20 mg/day	48% [†] (102/212)	47%* (103/219)
Naproxen 500 mg bid	44%* (100/225)	53% [†] (115/219)
Placebo	32% (70/222)	32% (71/220)

TABLE 2 ACR20 Response Rate (%) in Rheumatoid Arthritis		
	Study 1	Study 2
* p <0.01.		
† p <0.001 compared to placebo.		

Primary Dysmenorrhea

Valdecoxib was compared to naproxen sodium 550 mg in two placebo-controlled studies of women with moderate to severe primary dysmenorrhea. The onset of analgesia was within 60 minutes for valdecoxib 20 mg. The onset, magnitude, and duration of analgesic effect with valdecoxib 20 mg were comparable to naproxen sodium 550 mg.

Safety Studies

Gastrointestinal (GI) Endoscopy Studies With Therapeutic Doses

Scheduled upper GI endoscopic evaluations were performed with valdecoxib at doses of 10 and 20 mg daily in over 800 OA patients who were enrolled into two randomized 3 month studies using active comparators and placebo controls (Study 3 and Study 4). These studies enrolled patients free of endoscopic ulcers at baseline and compared rates of endoscopic ulcers, defined as any gastroduodenal ulcer seen endoscopically provided it was of "unequivocal depth" and at least 3 mm in diameter.

In both studies, valdecoxib 10 mg daily was associated with a statistically significant lower incidence of endoscopic gastroduodenal ulcers over the study period compared to the active comparators.

Safety Study With Supratherapeutic Doses

Scheduled upper GI endoscopic evaluations were performed in a randomized 6 month study of 1217 patients with OA and RA comparing valdecoxib 20 mg bid (40 mg daily) and 40 mg bid (80 mg daily) (4-8 times the recommended therapeutic dose) to naproxen 500 mg bid (Study 5). This study also formally assessed renal events as a primary outcome with supratherapeutic doses of valdecoxib. The renal endpoint was defined as any of the following: new/increase in edema, new/increase in congestive heart failure, increase in blood pressure (BP; >20 mm Hg systolic, >10 mm Hg diastolic), new/increase in BP treatment, new/ increase in diuretic therapy, creatinine increase over 30% (or >1.2 mg/dl if baseline <0.9 mg/dl), BUN increase over 200% or >50 mg/dl, 24 hour urinary protein increase to >500 mg (if baseline 0-150 mg or >750 if baseline 151-300 or >1000 if baseline 301-500), serum potassium increase to >6 mEq/L, or serum sodium decrease to <130 mEq/L.

Valdecoxib 40 mg daily and 80 mg daily were associated with a statistically significant lower incidence of endoscopic gastroduodenal ulcers over the study period compared to naproxen. The incidence of renal events was significantly different between the valdecoxib 80 mg daily group and naproxen. The clinical relevance of renal events observed with supratherapeutic doses (4-8 times the recommended therapeutic dose) of valdecoxib is not known (see [PRECAUTIONS, Renal Effects](#)).

Renal Safety at the Therapeutic Chronic Dose

The renal effects of valdecoxib compared with placebo and conventional NSAIDs were also assessed by prospectively designed pooled analyses of renal events data (see definition above — [Safety Study With Supratherapeutic Doses](#)) from five placebo- and active-controlled 12 week arthritis trials that included 995 OA or RA patients given valdecoxib 10 mg daily. The incidence of renal events observed in this analysis with valdecoxib 10 mg daily (3%), ibuprofen 800 mg tid (7%), naproxen 500 mg bid (2%) and diclofenac 75 mg bid (4%) were significantly higher than placebo-treated patients (1%). In all treatment groups, the majority of renal events were either due to the occurrence of edema or worsening BP.

Gastrointestinal Ulcers in High-Risk Patients

Subset analyses were performed of patients with risk factors (age, concomitant lowdose aspirin use, history of prior ulcer disease) enrolled in four upper GI endoscopic studies. [TABLE 3A](#) and [TABLE 3B](#) summarize the trends seen.

The correlation between findings of endoscopic studies, and the incidence of clinically significant serious upper GI events has not been established.

TABLE 3A Incidence of Endoscopic Gastroduodenal Ulcers in Patients With and Without Selected Risk Factors — Placebo-Controlled Studies		
		Valdecoxib (10-20 mg daily)
Risk Factor	Placebo	
Age		
<65 years	3.7% (8/219)	3.5% (17/484)
≥65 years	5.8% (8/137)	4.6% (12/262)
Concomitant Low Dose Aspirin Use		
No	4.4% (13/298)	3.2% (21/650)
Yes	5.2% (3/58)	8.3% (8/96)

TABLE 3A Incidence of Endoscopic Gastroduodenal Ulcers in Patients With and Without Selected Risk Factors — Placebo-Controlled Studies

		Valdecoxib (10-20 mg daily)
Risk Factor	Placebo	
History of Ulcer Disease		
No	4.4% (14/317)	3.4% (22/647)
Yes	5.1% (2/39)	7.1% (7/99)
No statistical conclusions can be drawn from these comparisons.		

TABLE 3B Incidence of Endoscopic Gastroduodenal Ulcers in Patients With and Without Selected Risk Factors — Active-Controlled Studies

Risk Factor	Valdecoxib 10-80 mg daily	Ibuprofen 800 mg tid	Naproxen 500 mg bid	Diclofenac 75 mg bid
Age				
<65 years	3.7% (48/1306)	8.2% (9/110)	12.8% (51/397)	13.2% (34/258)
≥65 years	7.6% (43/568)	21.6% (16/74)	22.0% (33/150)	18.2% (25/137)
Concomitant Low Dose Aspirin Use				
No	3.8% (64/1671)	9.8% (15/153)	16.0% (75/468)	12.8% (45/351)
Yes	13.3% (27/203)	32.3% (10/31)	11.4% (9/79)	31.8% (14/44)
History of Ulcer Disease				
No	4.1% (68/1666)	13.8% (22/160)	13.3% (63/475)	14.7% (52/354)
Yes	11.1% (23/208)	12.5% (3/24)	29.2% (21/72)	17.1% (7/41)
No statistical conclusions can be drawn from these comparisons.				

Platelets

In four clinical studies with young and elderly (≥65 years) subjects, single and multiple doses up to 7 days of valdecoxib 10-40 mg bid had no effect on platelet aggregation.

INDICATIONS AND USAGE:

Valdecoxib tablets are indicated:

For relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis.
For the treatment of primary dysmenorrhea.

CONTRAINDICATIONS:

Valdecoxib tablets are contraindicated in patients with known hypersensitivity to valdecoxib. Valdecoxib should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs are possible in such patients (see [WARNINGS, Anaphylactoid Reactions](#); and [PRECAUTIONS, Preexisting Asthma](#)).

WARNINGS:**Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation**

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine can occur at any time with or without warning symptoms in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor gastrointestinal problems such as dyspepsia are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms. Patients should be informed about the signs and symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation caused by NSAIDs appear to occur in approximately 1% of patients treated for 3-6 months and 2-4% of patients treated for 1 year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of

NSAID therapy, smoking, alcoholism, older age, and poor general health status. (See [CLINICAL STUDIES, Safety Studies](#).)

Anaphylactoid Reactions

Anaphylactoid reactions were not reported in patients receiving valdecoxib in clinical trials. However, as with NSAIDs in general, anaphylactoid reactions may occur in patients without known prior exposure to valdecoxib. Valdecoxib should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see [CONTRAINDICATIONS](#) and [PRECAUTIONS, Preexisting Asthma](#)). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

No information is available regarding the safe use of valdecoxib tablets in patients with advanced kidney disease. Therefore, treatment with valdecoxib is not recommended in these patients. If therapy with valdecoxib must be initiated, close monitoring of the patient's kidney function is advisable (see [PRECAUTIONS, Renal Effects](#)).

Pregnancy

In late pregnancy, valdecoxib should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS:

General

Valdecoxib tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of valdecoxib in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs. Notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may remain transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of valdecoxib, the incidence of borderline (defined as 1.2- to 3.0-fold) elevations of liver tests was 8.0% for valdecoxib and 8.4% for placebo, while approximately 0.3% of patients taking valdecoxib, and 0.2% of patients taking placebo, had notable (defined as greater than 3-fold) elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with valdecoxib. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash), valdecoxib should be discontinued.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and Angiotensin Converting Enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Caution should be used when initiating treatment with valdecoxib in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with valdecoxib. Caution is also recommended in patients with preexisting kidney disease. (See [WARNINGS, Advanced Renal Disease.](#))

Hematological Effects

Anemia is sometimes seen in patients receiving valdecoxib. Patients on long-term treatment with valdecoxib should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

Valdecoxib does not generally affect platelet counts, prothrombin time (PT), or partial prothrombin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (see [CLINICAL STUDIES, Safety Studies, Platelets](#)).

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking valdecoxib (see [ADVERSE REACTIONS](#)). Therefore, valdecoxib should be used with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, valdecoxib should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for the Patient

Valdecoxib can cause GI discomfort and, rarely, more serious GI side effects, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms.

Patients should be apprised of the importance of this follow-up (see [WARNINGS, Gastrointestinal \(GI\) Effects — Risk of GI Ulceration, Bleeding, and Perforation](#)).

Patients should report to their physicians, signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (*e.g.*, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and flu-like symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical attention.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see [WARNINGS, Anaphylactoid Reactions](#)).

In late pregnancy, valdecoxib should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs and symptoms of GI bleeding.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Valdecoxib was not carcinogenic in rats given oral doses up to 7.5 mg/kg/day for males and 1.5 mg/kg/day for females [equivalent to approximately 2- to 6-fold human exposure at 20 mg qd as measured by the AUC(0-24h)] or in mice given oral doses up to 25 mg/kg/day for males and 50 mg/kg/day for females [equivalent to approximately 0.6- to 2.4-fold human exposure at 20 mg qd as measured by the AUC(0-24h)] for 2 years.

Valdecoxib was not mutagenic in an Ames test or a mutation assay in Chinese hamster ovary (CHO) cells, nor was it clastogenic in a chromosome aberration assay in CHO cells or in an *in vivo* micronucleus test in rat bone marrow.

Valdecoxib did not impair male rat fertility at oral doses up to 9.0 mg/kg/day [equivalent to approximately 3- to 6-fold human exposure at 20 mg qd as measured by the AUC(0-24h)]. In female rats, a decrease in ovulation with increased pre- and post-implantation loss resulted in decreased live embryos/fetuses at doses ≥ 2 mg/kg/day (equivalent to approximately 2-fold human exposure at 20 mg qd as measured by the AUC(0-24h) for valdecoxib). The effects on female fertility were reversible. This effect is expected with inhibition of prostaglandin synthesis and is not the result of irreversible alteration of female reproductive function.

Pregnancy

Teratogenic Effects: Pregnancy Category C

The incidence of fetuses with skeletal anomalies such as semibipartite thoracic vertebrae and fused sternbrae was slightly higher in rabbits at an oral dose of 40 mg/kg/day [equivalent to approximately 72-fold human exposures at 20 mg qd as measured by the AUC(0-24h)] throughout organogenesis. Valdecoxib was not teratogenic in rabbits up to an oral dose of 10 mg/kg/day [equivalent to approximately 8-fold human exposures at 20 mg qd as measured by the AUC(0-24h)].

Valdecoxib was not teratogenic in rats up to an oral dose of 10 mg/kg/day [equivalent to approximately 19-fold human exposure at 20 mg qd as measured by the AUC(0-24h)]. There are no studies in pregnant women. However, valdecoxib crosses the placenta in rats and rabbits. Valdecoxib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Valdecoxib caused increased pre-and post-implantation loss with reduced live fetuses at oral doses ≥ 10 mg/kg/day [equivalent to approximately 19-fold human exposure at 20 mg qd as measured by the AUC(0-24h)] in rats and an oral dose of 40 mg/kg/day [equivalent to approximately 72-fold human exposure at 20 mg qd as measured by the AUC(0-24h)] in rabbits throughout organogenesis. In addition, reduced neonatal survival and decreased neonatal body weight when rats were treated with valdecoxib at oral doses ≥ 6 mg/kg/day [equivalent to approximately 7-fold human exposure at 20 mg qd as measured by the AUC(0-24h)] throughout organogenesis and lactation period. No studies have been conducted to evaluate the effect of valdecoxib on the closure of the ductus arteriosus in humans. Therefore, as with other drugs known to inhibit prostaglandin synthesis, use of valdecoxib during the third trimester of pregnancy should be avoided.

Labor and Delivery

Valdecoxib produced no evidence of delayed labor or parturition at oral doses up to 10 mg/kg/day in rats [equivalent to approximately 19-fold human exposure at 20 mg qd as measured by the AUC(0-24h)]. The effects of valdecoxib on labor and delivery in pregnant women are unknown.

Nursing Mothers

Valdecoxib and its active metabolite are excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for adverse reactions in nursing infants from valdecoxib, 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 and the importance of nursing to the infant.

Pediatric Use

Safety and effectiveness of valdecoxib in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the patients who received valdecoxib in arthritis clinical trials of 3 months duration, or greater, approximately 2100 were 65 years of age or older, including 570 patients who were 75 years or older. No overall differences in effectiveness were observed between these patients and younger patients.

DRUG INTERACTIONS:

The drug interaction studies with valdecoxib were performed both with valdecoxib and a rapidly hydrolyzed intravenous prodrug form. The results from trials using the intravenous prodrug are reported in this section as they relate to the role of valdecoxib in drug interactions.

General: In humans, valdecoxib metabolism is predominantly mediated via CYP 3A4 and 2C9 with glucuronidation being a further (20%) route of metabolism. *In vitro* studies indicate that valdecoxib is a moderate inhibitor of CYP 2C19 ($IC_{50} = 6 \mu\text{g/ml}$), and a weak inhibitor of both 3A4 ($IC_{50} = 44 \mu\text{g/ml}$) and 2C9 ($IC_{50} = 13 \mu\text{g/ml}$). In view of the limitations of *in vitro* studies and the high valdecoxib IC_{50} values, the potential for such metabolic inhibitory effects *in vivo* at therapeutic doses of valdecoxib is low.

Aspirin: Concomitant administration of aspirin with valdecoxib may result in an increased risk of GI ulceration and complications compared to valdecoxib alone. Because of its lack of anti-platelet effect valdecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

In a parallel group drug interaction study comparing the intravenous prodrug form of valdecoxib at 40 mg bid (n=10) vs placebo (n=9), valdecoxib had no effect on *in vitro* aspirin-mediated inhibition of arachidonate- or collagen-stimulated platelet aggregation.

Methotrexate: Valdecoxib 10 mg bid did not show a significant effect on the plasma exposure or renal clearance of methotrexate.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking valdecoxib concomitantly with ACE-inhibitors.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Anticonvulsants: Anticonvulsant drug interaction studies with valdecoxib have not been conducted. As with other drugs, routine monitoring should be performed when therapy with valdecoxib is either initiated or discontinued in patients on anticonvulsant therapy.

Dextromethorphan: Dextromethorphan is primarily metabolized by CYP 2D6 and to a lesser extent by 3A4. Coadministration with valdecoxib (40 mg bid for 7 days) resulted in a significant increase in dextromethorphan plasma levels suggesting that, at these doses, valdecoxib is a weak inhibitor of 2D6. Dextromethorphan plasma concentrations in the presence of high doses of valdecoxib were almost 5-fold lower than those seen in CYP 2D6 poor metabolizers.

Lithium: Valdecoxib 40 mg bid for 7 days produced significant decreases in lithium serum clearance (25%) and renal clearance (30%) with a 34% higher serum exposure compared to lithium alone. Lithium serum concentrations should be monitored closely when initiating or changing therapy with valdecoxib in patients receiving lithium. Lithium carbonate (450 mg bid for 7 days) had no effect on valdecoxib pharmacokinetics.

Warfarin: The effect of valdecoxib on the anticoagulant effect of warfarin (1-8 mg/day) was studied in healthy subjects by coadministration of valdecoxib 40 mg bid for 7 days. Valdecoxib caused a statistically significant increase in plasma exposures of R-warfarin and S-warfarin (12% and 15%, respectively), and in the pharmacodynamic effects (prothrombin time, measured as INR) of warfarin. While mean INR values were only

slightly increased with coadministration of valdecoxib, the day-to-day variability in individual INR values was increased. Anticoagulant therapy should be monitored, particularly during the first few weeks, after initiating therapy with valdecoxib in patients receiving warfarin or similar agents.

Fluconazole and Ketoconazole: Ketoconazole and fluconazole are predominantly CYP 3A4 and 2C9 inhibitors, respectively. Concomitant single dose administration of valdecoxib 20 mg with multiple doses of ketoconazole and fluconazole produced a significant increase in exposure of valdecoxib. Plasma exposure (AUC) to valdecoxib was increased 62% when coadministered with fluconazole and 38% when coadministered with ketoconazole.

Glyburide: Glyburide is a CYP 3A4 substrate. Coadministration of valdecoxib (10 mg bid for 7 days) with glyburide (5 mg qd or 10 mg bid) did not affect the pharmacokinetics (exposure) of glyburide.

ADVERSE REACTIONS:

Of the patients treated with valdecoxib tablets in controlled arthritis trials, 2665 were patients with OA, and 2684 were patients with RA. More than 4000 patients have received a chronic total daily dose of valdecoxib 10 mg or more. More than 2800 patients have received valdecoxib 10 mg/day, or more, for at least 6 months and 988 of these have received valdecoxib for at least 1 year.

Osteoarthritis and Rheumatoid Arthritis

[TABLE 4](#) lists all adverse events, regardless of causality, that occurred in $\geq 2.0\%$ of patients receiving valdecoxib 10 and 20 mg/day in studies of 3 months or longer from 7 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

In these placebo- and active-controlled clinical trials, the discontinuation rate due to adverse events was 7.5% for arthritis patients receiving valdecoxib 10 mg daily, 7.9% for arthritis patients receiving valdecoxib 20 mg daily and 6.0% for patients receiving placebo.

		Valdecoxib*		Diclofenac*	Ibuprofen*	Naproxen*
Adverse	Placebo	10 mg	20 mg	150 mg	2400 mg	1000 mg
Events	n=973	n=1214	n=1358	n=711	n=207	n=766

TABLE 4 Adverse Events With Incidence $\geq 2.0\%$ in Valdecoxib Treatment Groups: Controlled Arthritis Trials of 3 Months or Longer

		Valdecoxib*		Diclofenac*	Ibuprofen*	Naproxen*
Adverse	Placebo	10 mg	20 mg	150 mg	2400 mg	1000 mg
Events	n=973	n=1214	n=1358	n=711	n=207	n=766
Autonomic Nervous System Disorders						
Hypertension	0.6%	1.6%	2.1%	2.5%	2.4%	1.7%
Body as a Whole						
Back pain	1.6%	1.6%	2.7%	2.8%	1.4%	1.0%
Edema peripheral	0.7%	2.4%	3.0%	3.2%	2.9%	2.1%
Influenza-like symptoms	2.2%	2.0%	2.2%	3.1%	2.9%	2.0%
Injury accident	2.8%	4.0%	3.7%	3.9%	3.9%	3.0%
Central and Peripheral Nervous System Disorders						
Dizziness	2.1%	2.6%	2.7%	4.2%	3.4%	2.7%
Headache	7.1%	4.8%	8.5%	6.6%	4.3%	5.5%
Gastrointestinal System Disorders						
Abdominal fullness	2.0%	2.1%	1.9%	3.0%	2.9%	2.5%
Abdominal pain	6.3%	7.0%	8.2%	17.0%	8.2%	10.1%
Diarrhea	4.2%	5.4%	6.0%	10.8%	3.9%	4.7%
Dyspepsia	6.3%	7.9%	8.7%	13.4%	15.0%	12.9%
Flatulence	4.1%	2.9%	3.5%	3.1%	7.7%	5.4%
Nausea	5.9%	7.0%	6.3%	8.4%	7.7%	8.7%
Musculoskeletal System Disorders						
Myalgia	1.6%	2.0%	1.9%	2.4%	2.4%	1.4%
Respiratory System Disorders						
Sinusitis	2.2%	2.6%	1.8%	1.1%	3.4%	3.4%
Upper respiratory	6.0%	6.7%	5.7%	6.3%	4.3%	6.4%

TABLE 4 Adverse Events With Incidence $\geq 2.0\%$ in Valdecoxib Treatment Groups: Controlled Arthritis Trials of 3 Months or Longer

		Valdecoxib*		Diclofenac*	Ibuprofen*	Naproxen*
Adverse	Placebo	10 mg	20 mg	150 mg	2400 mg	1000 mg
Events	n=973	n=1214	n=1358	n=711	n=207	n=766
track infection						
Skin and Appendages Disorders						
Rash	1.0%	1.4%	2.1%	1.5%	0.5%	1.4%

* Total daily dose.

In the seven controlled OA and RA studies, the following adverse events occurred in 0.1-1.9% of patients treated with valdecoxib 10-20 mg daily, regardless of causality.

Application site disorders: Cellulitis, dermatitis contact.

Cardiovascular: Aggravated hypertension, aneurysm, angina pectoris, arrhythmia, cardiomyopathy, congestive heart failure, coronary artery disorder, heart murmur, hypotension.

Central, peripheral nervous system: Cerebrovascular disorder, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, tremor, twitching, vertigo.

Endocrine: Goiter.

Female reproductive: Amenorrhea, dysmenorrhea, leukorrhea, mastitis, menstrual disorder, menorrhagia, menstrual bloating, vaginal hemorrhage.

Gastrointestinal: Abnormal stools, constipation, diverticulosis, dry mouth, duodenal ulcer, duodenitis, eructation, esophagitis, fecal incontinence, gastric ulcer, gastritis, gastroenteritis, gastroesophageal reflux, hematemesis, hematochezia, hemorrhoids, hemorrhoids bleeding, hiatal hernia, melena, stomatitis, stool frequency increased, tenesmus, tooth disorder, vomiting.

General: Allergy aggravated, allergic reaction, asthenia, chest pain, chills, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, halitosis, malaise, pain, periorbital swelling, peripheral pain.

Hearing and vestibular: Ear abnormality, earache, tinnitus.

Heart rate and rhythm: Bradycardia, palpitation, tachycardia.

Hemic: Anemia.

Liver and biliary system: Hepatic function abnormal, hepatitis, ALT increased, AST increased.

Male reproductive: Impotence, prostatic disorder.

Metabolic and nutritional: Alkaline phosphatase increased, BUN increased, CPK increased, creatinine increased, diabetes mellitus, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperlipemia, hyperuricemia, hypocalcemia, hypokalemia, LDH increased, thirst increased, weight decrease, weight increase, xerophthalmia.

Musculoskeletal: Arthralgia, fracture accidental, neck stiffness, osteoporosis, synovitis,

tendonitis.

Neoplasm: Breast neoplasm, lipoma, malignant ovarian cyst.

Platelets (bleeding or clotting): Ecchymosis, epistaxis, hematoma NOS, thrombocytopenia.

Psychiatric: Anorexia, anxiety, appetite increased, confusion, depression, depression aggravated, insomnia, nervousness, morbid dreaming, somnolence.

Resistance mechanism disorders: Herpes simplex, herpes zoster, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media.

Respiratory: Abnormal breath sounds, bronchitis, bronchospasm, coughing, dyspnea, emphysema, laryngitis, pneumonia, pharyngitis, pleurisy, rhinitis.

Skin and appendages: Acne, alopecia, dermatitis, dermatitis fungal, eczema, photosensitivity allergic reaction, pruritus, rash erythematous, rash maculopapular, rash psoriaform, skin dry, skin hypertrophy, skin ulceration, sweating increased, urticaria.

Special senses: Taste perversion.

Urinary system: Albuminuria, cystitis, dysuria, hematuria, micturition frequency increased, pyuria, urinary incontinence, urinary tract infection.

Vascular: Claudication intermittent, hemangioma acquired, varicose vein.

Vision: Blurred vision, cataract, conjunctival hemorrhage, conjunctivitis, eye pain, keratitis, vision abnormal.

White cell and RES disorders: Eosinophilia, leukopenia, leukocytosis, lymphadenopathy, lymphangitis, lymphopenia.

Other serious adverse events that were reported rarely (estimated <0.1%) in clinical trials, regardless of causality, in patients taking valdecoxib:

Autonomic nervous system disorders: Hypertensive encephalopathy, Vasospasm.

Cardiovascular: Abnormal ECG, aortic stenosis, atrial fibrillation, carotid stenosis, coronary thrombosis, heart block, heart valve disorders, mitral insufficiency, myocardial infarction, myocardial ischemia, pericarditis, syncope, thrombophlebitis, unstable angina, ventricular fibrillation.

Central, peripheral nervous system: Convulsions.

Endocrine: Hyperparathyroidism.

Female reproductive: Cervical dysplasia.

Gastrointestinal: Appendicitis, colitis with bleeding, dysphagia, esophageal perforation, gastrointestinal bleeding, ileus, intestinal obstruction, peritonitis.

Hemic: Lymphoma-like disorder, pancytopenia.

Liver and biliary system: Cholelithiasis.

Metabolic: Dehydration.

Musculoskeletal: Pathological fracture, osteomyelitis.

Neoplasm: Benign brain neoplasm, bladder carcinoma, carcinoma, gastric carcinoma, prostate carcinoma, pulmonary carcinoma.

Platelets (bleeding or clotting): Embolism, pulmonary embolism, thrombosis.

Psychiatric: Manic reaction, psychosis.

Renal: Acute renal failure.

Resistance mechanism disorders: Sepsis.

Respiratory: Apnea, pleural effusion, pulmonary edema, pulmonary fibrosis, pulmonary infarction, pulmonary hemorrhage, respiratory insufficiency.

Skin: Basal cell carcinoma, malignant melanoma.

Urinary system: Pyelonephritis, renal calculus.

Vision: Retinal detachment.

OVERDOSAGE:

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare.

Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Hemodialysis removed only about 2% of administered valdecoxib from the systemic circulation of 8 patients with end-stage renal disease and, based on its degree of plasma protein binding (>98%), dialysis is unlikely to be useful in overdose. Forced diuresis, alkalization of urine, or hemoperfusion also may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION:

Osteoarthritis and Adult Rheumatoid Arthritis

The recommended dose of valdecoxib tablets for the relief of the signs and symptoms of arthritis is 10 mg once daily.

Primary Dysmenorrhea

The recommended dose of valdecoxib tablets for treatment of primary dysmenorrhea is 20 mg twice daily, as needed.

HOW SUPPLIED:

Bextra tablets are available in:

10 mg: White, film-coated, and capsule-shaped, debossed "10" on one side with a four

pointed star shape on the other.

20 mg: White, film-coated, and capsule-shaped, debossed "20" on one side with a four pointed star shape on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Hydroxychloroquine Sulfate (001506)

CATEGORIES:

Indications: Arthritis, rheumatoid; Lupus erythematosus, chronic discoid; Lupus erythematosus, systemic; Malaria

Pregnancy Category C

FDA Approved 1955 Apr

DRUG CLASS: Antiprotozoals; Disease modifying antirheumatic drugs

BRAND NAMES: *Dimard* (Colombia); *Ercoquin* (Denmark, Norway, Japan); *Geniquin* (Taiwan); *Haloxin* (Korea); *Oxiklorin* (Finland, Korea); **Plaquenil (US)**; *Plaquenil Sulfate* (Canada); *Plaquinol* (Costa-Rica, Dominican-Republic, El-Salvador, Guatemala, Honduras, Nicaragua, Panama, Colombia, Peru, Portugal); *Quensyl* (Germany); *Toremonil* (Japan); *Yuma* (Korea); *(International brand names outside U.S. in italics)*

COST OF THERAPY:	Price	Indication	Form	Strength	Per Day	Days of Therapy
	\$ 14.67	Malaria Treatment	Plaquenil	200 mg	10 tablets	variable
	\$ 10.00	Malaria Treatment	Generic Tablets	200 mg	10 tablets	variable
	\$ 44.01	Rheumatoid Arthritis	Plaquenil	200 mg	1 tablet/day	30
	\$ 30.00	Rheumatoid Arthritis	Generic Tablets	200 mg	1 tablet/day	30

WARNING:

PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS LEAFLET BEFORE PRESCRIBING **HYDROXYCHLOROQUINE**.

DESCRIPTION:

Hydroxychloroquine sulfate is a colorless crystalline solid, soluble in water to at least 20%; chemically the drug is 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]ethylamino]ethanol sulfate (1:1). Plaquenil (**hydroxychloroquine** sulfate) tablets contain 200 mg **hydroxychloroquine** sulfate, equivalent to 155 mg base, and are for oral administration.

Inactive Ingredients: Dibasic calcium phosphate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 400, polysorbate 80, starch, titanium dioxide.

CLINICAL PHARMACOLOGY:

Actions

The drug possesses antimalarial actions and also exerts a beneficial effect in lupus erythematosus (chronic discoid or systemic) and acute or chronic rheumatoid arthritis. The precise mechanism of action is not known.

Malaria

Like chloroquine phosphate, **hydroxychloroquine** sulfate is highly active against the erythrocytic forms of *Plasmodium vivax* and *malariae* and most strains of *P. falciparum* (but not the gametocytes of *P. falciparum*). **Hydroxychloroquine** sulfate does not prevent relapses in patients with *vivax* or *malariae* malaria because it is not effective against exo-erythrocytic forms of the parasite, nor will it prevent *vivax* or *malariae* infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with *vivax* or *malariae* malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with *falciparum* malaria, it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum*.

INDICATIONS AND USAGE:

Hydroxychloroquine sulfate is indicated for the suppressive treatment and treatment of acute attacks of malaria due to *Plasmodium vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of discoid and systemic lupus erythematosus, and rheumatoid arthritis.

Malaria

Hydroxychloroquine sulfate is indicated for the treatment of acute attacks and suppression of malaria.

Lupus Erythematosus and Rheumatoid Arthritis

Hydroxychloroquine sulfate is useful in patients with the following disorders who have not responded satisfactorily to drugs with less potential for serious side effects: lupus erythematosus (chronic discoid and systemic) and acute or chronic rheumatoid arthritis.

CONTRAINDICATIONS:

Use of this drug is contraindicated (1) in the presence of retinal or visual field changes attributable to any 4-aminoquinoline compound, (2) in patients with known hypersensitivity to 4-aminoquinoline compounds, and (3) for long-term therapy in children.

WARNINGS:

General

Hydroxychloroquine sulfate is not effective against chloroquine-resistant strains of *P. falciparum*.

Children are especially sensitive to the 4-aminoquinoline compounds. A number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 or 1 g in one 3-year-old child). Patients should be strongly warned to keep these drugs out of the reach of children.

Use of **hydroxychloroquine** sulfate in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria the condition may be exacerbated. The preparation should not be used in these conditions unless in the judgment of the physician the benefit to the patient outweighs the possible hazard.

Use in Pregnancy

Usage of this drug during pregnancy should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the possible hazard. It should be noted that radioactively-tagged chloroquine administered intravenously to pregnant, pigmented CBA mice passed rapidly across the placenta. It accumulated selectively in the melanin structures of the fetal eyes and was retained in the ocular tissues for 5 months after the drug had been eliminated from the rest of the body.

Malaria

In recent years, it has been found that certain strains of *P. falciparum* have become resistant to 4-aminoquinoline compounds (including **hydroxychloroquine**) as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia. Treatment with quinine or other specific forms of therapy is therefore advised for patients infected with a resistant strain of parasites.

Lupus Erythematosus and Rheumatoid Arthritis

PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS PRESCRIBING INFORMATION BEFORE PRESCRIBING **HYDROXYCHLOROQUINE** SULFATE.

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinoline therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis. Retinopathy has been reported to be dose-related.

When prolonged therapy with any antimalarial compound is contemplated, initial (base line) and periodic (every 3 months) ophthalmologic examinations (including visual acuity, expert slit-lamp, funduscopy, and visual field tests) should be performed.

If there is any indication of abnormality in the visual acuity, visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) which are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress even after cessation of therapy.

All patients on long-term therapy with this preparation should be questioned and examined periodically, including the testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug.

In the treatment of rheumatoid arthritis, if objective improvement (such as reduced joint swelling, increased mobility) does not occur within 6 months, the drug should be discontinued.

Safe use of the drug in the treatment of juvenile arthritis has not been established.

PRECAUTIONS:

General

Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs.

Periodic blood cell counts should be made if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuation of the drug should be considered. The drug should be administered with caution in patients having G-6-PD (glucose-6-phosphate dehydrogenase) deficiency.

Lupus Erythematosus and Rheumatoid Arthritis

Dermatologic reactions to **hydroxychloroquine** sulfate may occur and, therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis.

The methods recommended for early diagnosis of "chloroquine retinopathy" consist of (1) funduscopic examination of the macula for fine pigmentary disturbances or loss of the foveal reflex and (2) examination of the central visual field with a small red test object for pericentral or paracentral scotoma or determination of retinal thresholds to red. Any unexplained visual symptoms, such as light flashes or streaks should also be regarded with suspicion as possible manifestations of retinopathy. If serious toxic symptoms occur from overdosage or sensitivity, it has been suggested that ammonium chloride (8 g daily in divided doses for adults) be administered orally 3 or 4 days a week for several months after therapy has been stopped, as acidification of the urine increases renal excretion of the 4-aminoquinoline compounds by 20-90%. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

ADVERSE REACTIONS:

Malaria

Following the administration in doses adequate for the treatment of an acute malarial attack, mild and transient headache, dizziness, and gastrointestinal complaints (diarrhea, anorexia, nausea, abdominal cramps and, on rare occasions, vomiting) may occur.

Cardiomyopathy has been rarely reported with high daily dosages of **hydroxychloroquine**.

Lupus Erythematosus and Rheumatoid Arthritis

Not all of the following reactions have been observed with every 4-aminoquinoline compound during long-term therapy, but they have been reported with one or more and should be borne in mind when drugs of this class are administered. Adverse effects with different compounds vary in type and frequency.

CNS Reactions: Irritability, nervousness, emotional changes, nightmares, psychosis, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia.

Neuromuscular Reactions: Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups which may be associated with mild sensory changes, depression of tendon reflexes and abnormal nerve conduction.

Ocular Reactions:

Ciliary Body: Disturbance of accommodation with symptoms of blurred vision. This reaction is dose-related and reversible with cessation of therapy.

Cornea: Transient edema, punctate to lineal opacities, decreased corneal sensitivity. The corneal changes, with or without accompanying symptoms (blurred vision, halos around lights, photophobia), are fairly common, but reversible. Corneal deposits may appear as early as 3 weeks following initiation of therapy.

The incidence of corneal changes and visual side effects appears to be considerably lower with **hydroxychloroquine** than with chloroquine.

Retina: Macula: Edema, atrophy, abnormal pigmentation (mild pigment stippling to a "bull's-eye" appearance), loss of foveal reflex, increased macular recovery time following exposure to a bright light (photo-stress test), elevated retinal threshold to red light in macular, paramacular, and peripheral retinal areas.

Other fundus changes include optic disc pallor and atrophy, attenuation of retinal arterioles, fine granular pigmentary disturbances in the peripheral retina and prominent choroidal patterns in advanced stage.

Visual Field Defects: Pericentral or paracentral scotoma, central scotoma with decreased-visual acuity, rarely field constriction.

The most common visual symptoms attributed to the retinopathy are: reading and seeing difficulties (words, letters, or parts of objects missing), photophobia, blurred distance vision, missing or blacked out areas in the central or peripheral visual field, light flashes and streaks.

Retinopathy appears to be dose related and has occurred within several months (rarely) to several years of daily therapy; a small number of cases have been reported several years after antimalarial drug therapy was discontinued. It has not been noted during prolonged use of weekly doses of the 4-aminoquinoline compounds for suppression of malaria.

Patients with retinal changes may have visual symptoms or may be asymptomatic (with or without visual field changes). Rarely scotomatous vision or field defects may occur without obvious retinal change.

Retinopathy may progress even after the drug is discontinued. In a number of patients, early retinopathy (macular pigmentation sometimes with central field defects) diminished or regressed completely after therapy was discontinued. Paracentral scotoma to red targets (sometimes called "premaculopathy") is indicative of early retinal dysfunction which is usually reversible with cessation of therapy.

A small number of cases of retinal changes have been reported as occurring in patients who received only **hydroxychloroquine**. These usually consisted of alteration in retinal pigmentation which was detected on periodic ophthalmologic examination; visual field defects were also present in some instances. A case of delayed retinopathy has been reported with loss of vision starting 1 year after administration of **hydroxychloroquine** had been discontinued.

- **Dermatologic Reactions:** Bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and exfoliative dermatitis).
- **Hematologic Reactions:** Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6-PD) deficiency).
- **Gastrointestinal Reactions:** Anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Isolated cases of abnormal liver function and fulminant hepatic failure.
- **Miscellaneous Reactions:** Weight loss, lassitude, exacerbation or precipitation of porphyria and nonlight-sensitive psoriasis.
- Cardiomyopathy has been rarely reported with high daily dosages of **hydroxychloroquine**.

OVERDOSAGE:

The 4-aminoquinoline compounds are very rapidly and completely absorbed after ingestion, and in accidental overdose, or rarely with lower doses in hypersensitive patients, toxic symptoms may occur within 30 minutes. These consist of headache, drowsiness, visual disturbances, cardiovascular collapse, and convulsions, followed by sudden and early respiratory and cardiac arrest. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest. Treatment is symptomatic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital) or gastric lavage until the stomach is completely emptied. If finely powdered, activated charcoal is introduced by the stomach tube, after lavage, and within 30 minutes after ingestion of the tablets, it may inhibit further intestinal absorption of the drug. To be effective, the dose of activated charcoal should be at least 5 times the estimated dose of **hydroxychloroquine** ingested. Convulsions, if present, should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultrashort-acting barbiturate may be tried but, if due to anoxia, it should be corrected by oxygen administration, artificial respiration or, in shock with hypotension, by vasopressor therapy. Because of the importance of supporting respiration, tracheal intubation or tracheostomy, followed by gastric lavage, may also be necessary. Exchange transfusions have been used to reduce the level of 4-aminoquinoline drug in the blood.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least 6 hours. Fluids may be forced, and sufficient ammonium chloride (8 g daily in divided doses for adults) may be administered for a few days to acidify the urine to help promote urinary excretion in cases of both overdose and sensitivity.

DOSAGE AND ADMINISTRATION:

One (1) tablet of 200 mg of **hydroxychloroquine** sulfate is equivalent to 155 mg base.

Malaria **Suppression**

In adults, 400 mg (= 310 mg base) on exactly the same day of each week. *In infants and children*, the weekly suppressive dosage is 5 mg, calculated as base, per kg of body weight, but should not exceed the adult dose regardless of weight.

If circumstances permit, suppressive therapy should begin 2 weeks prior to exposure.

However, failing this, in adults an initial double (loading) dose of 800 mg (= 620 mg base), or in children 10 mg base/kg may be taken in 2 divided doses, 6 hours apart. The suppressive therapy should be continued for 8 weeks after leaving the endemic area.

Treatment of the Acute Attack

In adults, an initial dose of 800 mg (= 620 mg base) followed by 400 mg (= 310 mg base) in 6-8 hours and 400 mg (= 310 mg base) on each of 2 consecutive days (total 2 g **hydroxychloroquine** sulfate or 1.55 g base). An alternative method, employing a single dose of 800 mg (= 620 mg base), has also proved effective.

The dosage for adults may also be calculated on the basis of body weight; this method is preferred for infants and children.

A total dose representing 25 mg of base per kg of body weight is administered in 3 days, as follows:

First Dose: 10 mg base per kg (but not exceeding a single dose of 620 mg base).

Second Dose: 5 mg base per kg (but not exceeding a single dose of 310 mg base) 6 hours after first dose.

Third Dose: 5 mg base per kg 18 hours after second dose.

Fourth Dose: 5 mg base per kg 24 hours after third dose.

For radical cure of *vivax* and *malariae* malaria concomitant therapy with an 8-aminoquinoline compound is necessary.

Lupus Erythematosus and Rheumatoid Arthritis

One (1) tablet of **hydroxychloroquine** sulfate, 200 mg, is equivalent to 155 mg base.

Lupus Erythematosus

Initially, the average *adult* dose is 400 mg (= 310 mg base) once or twice daily. This may be continued for several weeks or months, depending on the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200-400 mg (155-310 mg base) daily will frequently suffice.

The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Rheumatoid Arthritis

The compound is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur relatively early.

Several months of therapy may be required before maximum effects can be obtained. If objective improvement (such as reduced joint swelling, increased mobility) does not occur within 6 months, the drug should be discontinued. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Initial Dosage

In adults, from 400-600 mg (= 310-465 mg base) daily, each dose to be taken with a meal or a glass of milk. In a small percentage of patients, troublesome side effects may require temporary reduction of the initial dosage. Later (usually from 5-10 days), the dose may gradually be increased to the optimum response level, often without return of side effects.

Maintenance Dosage

When a good response is obtained (usually in 4-12 weeks), the dosage is reduced by 50% and continued at a usual maintenance level of 200-400 mg (= 155-310 mg base) daily, each dose to be taken with a meal or a glass of milk. The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded. Should a relapse occur after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.

Corticosteroids and salicylates may be used in conjunction with this compound, and they can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. When gradual reduction of steroid dosage is indicated, it may be done by reducing every 4-5 days the dose of cortisone by no more than from 5-15 mg; of hydrocortisone from 5-10 mg; of prednisolone and prednisone from 1-2.5 mg; of

methylprednisolone and triamcinolone from 1-2 mg; and of dexamethasone from 0.25-0.5 mg.

HOW SUPPLIED:

Plaquenil tablets are white, to off-white, film coated tablets imprinted "PLAQUENIL" on one face in black ink. Each tablet contains 200 mg **hydroxychloroquine** sulfate (equivalent to 155 mg base).

Storage: Dispense in a tight, light-resistant container. Store at room temperature up to 30°C (86°F).