

## **ETANERCEPT - ENBREL™ (Immunex Corp.; Wyeth-Ayerst Laboratories) 1P**

**INDICATIONS:** Etanercept is approved for the treatment of moderately to severely active rheumatoid arthritis in patients who have failed disease-modifying antirheumatic drugs (DMARDs). It can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone. It is also being evaluated for the treatment of early-stage, rheumatoid arthritis in adults, juvenile rheumatoid arthritis, prevention of muromonab-CD3-associated acute clinical syndrome, heart failure, organ transplantation and cachexia.

**CLINICAL PHARMACOLOGY:** Rheumatoid arthritis is a chronic inflammatory and debilitating disease that affects 0.5% to 1% of the population. Traditional therapy (eg, nonsteroidal anti-inflammatory agents) has been directed at providing palliative therapy and slowing the course of the disease (eg, methotrexate, d-penicillamine, gold, hydroxychloroquine), but nothing has been able to stop the disease or reverse the damage. Newer forms of therapy have been directed at modifying the inflammatory mediators (eg, interleukins, tumor necrosis factor [TNF], transforming growth factor) associated with this disease.

Etanercept is a soluble recombinant human TNF receptor p75 Fc fusion protein that binds and neutralizes TNF biological activity. Etanercept is produced using recombinant DNA technology in a Chinese hamster ovary mammalian expression system. The cells express etanercept, and etanercept is 2 p75 TNFR fused to the Fc portion of IgG1. The final molecule is a dimer consisting of two TNF receptor molecules per Fc molecule. Infliximab is a chimeric-murine monoclonal TNF antibody approved for the acute treatment of Crohn's disease. Etanercept can prevent inflammation by binding the soluble TNF $\alpha$  and TNF $\beta$  (lymphotoxin alpha [LT $\alpha$ ]), a proinflammatory cytokine. If the TNF is allowed to bind to cell-surface binding sites, it induces the proliferation of synoviocytes (the fibroblast-like cells that line the joint) and enhances the production of prostaglandins, metalloproteinases and cytokines. Both drugs, work by binding the TNF and by preventing binding to cellular receptors. By decreasing the amount of soluble TNF, the drugs decrease joint swelling, tenderness and morning stiffness and lower the levels of C-reactive protein, erythrocyte sedimentation rate and blood cytokines. Cells expressing transmembrane TNF that bind etanercept are not lysed *in vitro* in the presence or absence of complement, whereas they are with infliximab.

**PHARMACOKINETICS:** The bioavailability of etanercept, following subcutaneous administration, is 58%. Peak plasma concentrations occur at 48 to 96 hours and are 81.5% lower than those achieved following intravenous administration. The volume of distribution following intravenous administration ranges from 1.78 to 3.39 L/m<sup>2</sup>. The half-life ranges from 57.9 to 84.6 hours following intravenous administration and is 98 to 300 hours following subcutaneous administration.

No differences in any pharmacokinetic parameters were observed in men, women, age or pediatric patients. The effects of renal and hepatic dysfunction on etanercept's pharmacokinetics have not been evaluated.

### **CLINICAL EFFICACY:**

*Rheumatoid Arthritis, Advanced:* The FDA-approved indication for etanercept is the treatment of moderately to severely active rheumatoid arthritis in patients who have failed DMARDs. In short-term effectiveness trials, etanercept improved function, decreased joint pain and swelling and improved the patient's functional ability and decreased morning stiffness and fatigue.

A multicenter, double-blind, placebo controlled study enrolled 180 patients with refractory rheumatoid arthritis to evaluate the safety and effectiveness of etanercept. Patients were required to be 18 years or older with a diagnosis of rheumatoid arthritis, based on the American Rheumatism Association criteria; be classified as functional class I, II or III by the American College of Rheumatology criteria; have failed therapy with at least one but not more than four DMARDs (eg, hydroxychloroquine, oral or injectable gold, methotrexate, azathioprine, penicillamine and sulfasalazine); and have stable doses of NSAID or corticosteroids for at least 4 weeks before the washout period and throughout the study and follow-up.

The DMARD therapy had to be discontinued at least 4 weeks prior to receiving the study drug. In addition, the patient had to have a hemoglobin level of  $\geq 8.5/L$ , platelet count of  $\geq 125,000/mm^3$ , white-cell count  $\geq 3500/mm^3$ , serum creatinine level of  $\leq 2$  mg/dL and liver aminotransferase levels  $< 2$  times the upper limit of normal. Patients were randomly assigned to treatment with placebo, etanercept 0.25 mg/m<sup>2</sup> body surface area (BSA), etanercept 2 mg/m<sup>2</sup> BSA or etanercept 16 mg/m<sup>2</sup> BSA. The placebo was the same lyophilized powder as the etanercept formulation minus the drug. The lyophilized powder was diluted with bacteriostatic water for injection and the injection volume was standardized so that all patients received two 1.5 mL injections per dose. The drug was administered in the mornings by subcutaneous injections twice a week for 3 months. The patients were allowed to continue their NSAID or corticosteroid therapy throughout the study period but the dose had to remain the same. If supplemental analgesia was needed, it could be done with acetaminophen with codeine phosphate, acetaminophen with propoxyphene napsylate or acetaminophen with oxycodone hydrochloride, except on the day before a joint evaluation. The mean age of the study population was 53 years, with 77% having had the disease for at least 5 years. More women (n=132) were enrolled than men (n=48), and most patients were Caucasian. The completion rate in the placebo group was 52%, etanercept 0.25 mg/m<sup>2</sup> group was 61%, etanercept 2 mg/m<sup>2</sup> group was 78% and etanercept 16 mg/m<sup>2</sup> group was 93%. The primary reason for not completing the study was inadequate control of the arthritis symptoms: 43%, 35%, 17% and 5%, respectively. The best clinical improvements (eg, decreased number of swollen and painful joints, duration of morning stiffness and improvement in quality of life) were reported in the group treated with the etanercept 16 mg/m<sup>2</sup> (see Table 1 and Figures 1 and 2), and the difference in response was notable within 2 weeks of starting therapy. Discontinuation of the etanercept therapy resulted in return of arthritis symptoms within 1 month.

Table 1: Improvement in Rheumatoid Arthritis After 3 Months of Etanercept or Placebo Therapy:

Disease Parameter	Placebo	Etanercept 0.25 mg/m <sup>2</sup>	Etanercept 2 mg/m <sup>2</sup>	Etanercept 16 mg/m <sup>2</sup>
	n=44	n=46	n=46	n=44
Swollen-Joint Count	17	19	17	11
<i>Improvement from baseline</i>	24%	16%	32%	58%
Tender-Joint Count	22	24	17	13
<i>Improvement from baseline</i>	28%	25%	46%	64%
Morning Stiffness	4.1 hours	5.3 hours	2.6 hours	1.1 hours
Physician=s Assessment*	5.9	5.6	4.3	2.7
Patient=s Assessment*	6.2	5.8	4.6	3.2
Pain B Visual Analog Scale*	6.1	5.6	4.6	3.1
Quality of Life (health-assessment questionnaire)**	141	137	123	104
Erythrocyte Sedimentation Rate (mm/hr)	40	39	27	21
C-reactive Protein (mg/dL)	2.6	2.4	2	0.9

\* = Based on a scale where 0 is the best and 10 is the worst.

\*\* = Based on a scale where 45 is the best and 245 is the worst.

Figure 1: Improvement (20%) in Rheumatoid Arthritis Based on American College of Rheumatology Criteria (ACR) Following 3 Months of Therapy with Placebo and Etanercept:

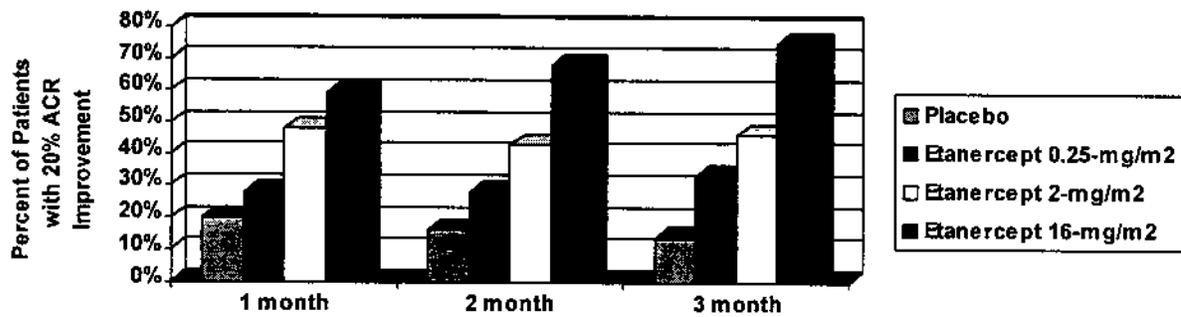
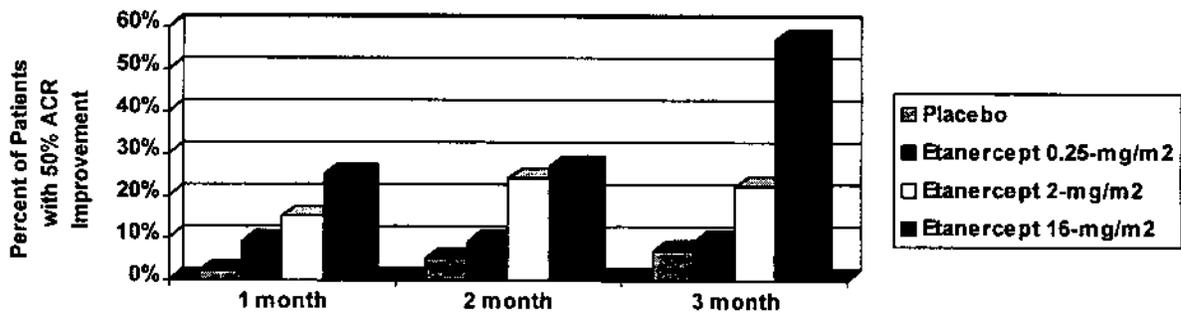


Figure 2: Improvement (50%) in Rheumatoid Arthritis Based on American College of Rheumatology Criteria Following 3 Months of Therapy with Placebo and Etanercept.<sup>25</sup>



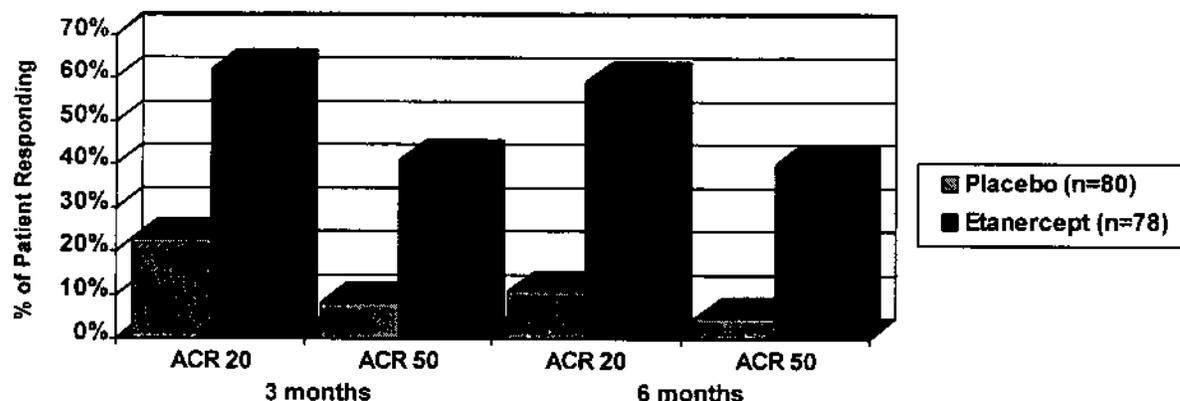
The product labeling contains the results of a similar study where patients were treated with either placebo, etanercept 10 mg or etanercept 25 mg (approximately equivalent to 16 mg/m<sup>2</sup>). This study enrolled 234 patients. A clinical response generally occurred within 2 weeks. Like the previously reported results, the percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria improved over time; with more patients achieving 50% and 70% improvement the longer the etanercept therapy was used (see Table 2 and Figure 3). The maximum benefit in all disease parameters, including the Health Assessment Questionnaire, were achieved with etanercept 25 mg. Age did not influence the clinical benefit derived from the etanercept therapy.

Table 2: Improvement in Rheumatoid Arthritis After 3 Months of Etanercept or Placebo Therapy:

Disease Parameter	Placebo n=80		Etanercept 25 mg n=78	
	Baseline	3 Months	Baseline	3 Months
Swollen-Joint Count	24	22	23.5	12.6
<i>Improvement from baseline</i>		8.3%		46.4%
Tender-Joint Count	34	29.5	31.2	10
<i>Improvement from baseline</i>		13.2%		68%
Physician=s Assessment*	7	6.5	7	3
<i>Improvement from baseline</i>		7.1%		57.1%
Patient=s Assessment*	7	7	7	3
<i>Improvement from baseline</i>		0%		57.1%
Pain B Visual Analog Scale*	6.9	6.6	6.9	2.4
<i>Improvement from baseline</i>		4.4%		65.2%
Erythrocyte Sedimentation Rate (mm/hr)	31	32	28	15.5
<i>Improvement from baseline</i>		-3.2%		44.6%
C-reactive Protein (mg/dL)	2.8	3.9	3.5	0.9
<i>Improvement from baseline</i>		-39.3%		74.3%

\* = Based on a visual analog scale where 0 is the best and 10 is the worst.

Figure 3: Improvement in Rheumatoid Arthritis Based on American College of Rheumatology Criteria Following Therapy with Placebo and Etanercept 25 mg:

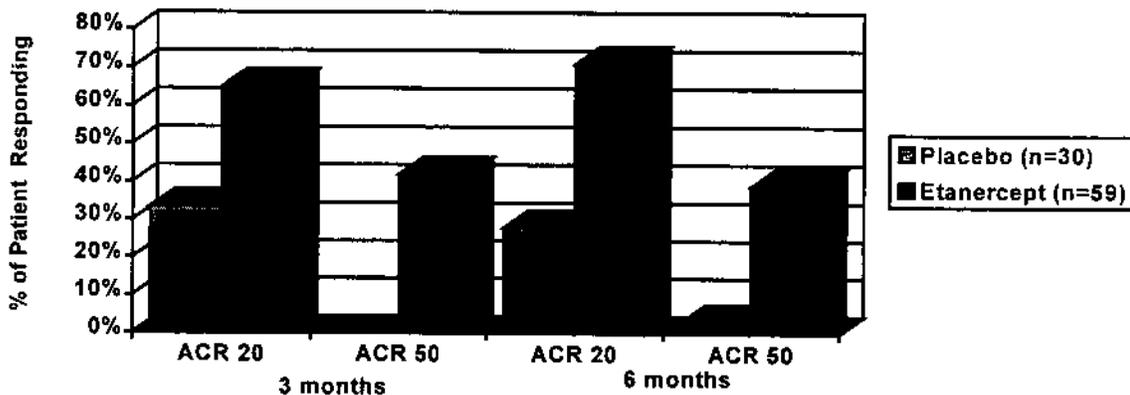


The second study described in the product labeling used similar inclusion criteria plus the patients had received methotrexate for at least 6 months with a stable dose (12.5 to 25 mg/week). In addition, the patients had to have at least 6 tender or painful joints. These patients (n=89) continued their methotrexate therapy and were given a 25 mg dose of etanercept or placebo subcutaneously twice a week for 6 months. Eighty-one patients completed the study; 24 treated with placebo (80%) and 57 treated with etanercept (97%). The placebo patients discontinued the study drug because of lack of efficacy (n=4), intercurrent illness (n=1) and lost to follow-up (n=1). The etanercept patients discontinued the study drug only because of an intercurrent illness (n=2). See Table 3 and Figure 4 for the results of this study.

Table 3: Median Improvement in the Measure of Rheumatoid Arthritis Parameters with Methotrexate Plus Placebo or Etanercept:

Parameter	Placebo/Methotrexate (n=30)		Etanercept/Methotrexate (n=59)	
	Baseline	6 Months	Baseline	6 Months
Physician assessment (0-10)	6.5	4	6	2
Patient assessment (0-10)	6	4	6	2
Pain B VAS (0-10)	5.6	4.4	5	1.8
HAQ disability (0-3)	1.5	1.1	1.5	0.8
C-reactive protein (mg/dL)	2.6	1.6	2.2	0.5

Figure 4: Improvement in Rheumatoid Arthritis Based on American College of Rheumatology Criteria Following Therapy with Methotrexate Plus Placebo or Etanercept:



An open-labeled, long-term trial of etanercept in the treatment of active rheumatoid arthritis was conducted with 105 patients. All of the patients had previously been treated with etanercept for a maximum of 3 months. The average time between treatment regimens was 17 months (range 1 to 34 months). The dose of etanercept used in this trial was 25 mg subcutaneously twice a week for up to 6 months. At the time the data were summarized, 85 patients had received the etanercept therapy for 6 months. This group was 76% female; 88% had previously been treated with methotrexate, their mean age was 53 years and the mean duration of disease was 12 years. After the 6 months of therapy, 74% had a  $\geq 50\%$  improvement in joint tenderness and 62% had a similar improvement in joint swelling. Table 4 is a summary of the improvement seen in other disease parameters. Eighty-eight patients have received etanercept for 12 months, 79 patients have reached 18 months and 51 patients have reached 24 months. These data indicate that the drug is well tolerated and 80% of those treated for 24 months achieved at least a 20% Paulus response. In addition, 83 patients have been treated for at least 24 months with continued efficacy. Twenty-two patients discontinued etanercept therapy; seven were patient requested, six because of lack of efficacy, five had adverse effects, three were protocol deviation and one was lost to follow-up.

Table 4: Median Improvement in Rheumatoid Arthritis Disease Parameters with Etanercept in an Open-Labelled Study:

	Baseline (n=85)	2 Weeks (n=84)	1 Month (n=84)	3 Months (n=82)	6 Months (n=78)
# Tender Joints	31	16	14	6	9
# Swollen Joints	25	19	14	11	9
Duration of Morning Stiffness (minutes)	150	60	30	30	30
C-reactive protein (mg/dL)	2.9	0.9	0.8	0.8	0.9

*Other Potential Uses:*

*Juvenile Rheumatoid Arthritis (JRA):* Improvement in joint swelling and pain also occurs in children and teenagers (4 to 17 years) with juvenile rheumatoid arthritis after treatment with etanercept. These patients had active polyarticular course juvenile rheumatoid arthritis that was refractory or intolerant to methotrexate therapy. Children (n=69) were treated with etanercept in an open-labeled study. All other forms of DMARD therapy were discontinued at least 1 month before etanercept, except methotrexate that was discontinued 2 weeks prior to therapy. The dose used in this study was 0.4 mg/kg subcutaneously, with a maximum of 25 mg/dose twice weekly for 90 days. Patients were allowed to use a single NSAID and low-dose prednisone (<0.2 mg/kg/day; 10 mg/day maximum) throughout the study as long as the doses remained stable. A positive clinical response was classified as a  $\geq 30\%$  improvement in at least 3 of the 6 juvenile rheumatoid arthritis core set variables and no greater than one variable worsening by 30% or more. The preliminary data from 54 children treated for 90 days showed a median improvement in number of active joints of 60%, number of joints with loss of motion of 80%, morning stiffness improvement in 76%, erythrocyte sedimentation rate decrease from 33 mm/h to 16 mm/h (54%) and median visual analog score decrease from 3.5 to 1.3 (70%). The follow-up data on this study are summarized in Table 5. Etanercept responders were then invited to participate in a follow-up double-blind, placebo controlled study. These patients were randomly assigned to treatment with etanercept or placebo for 4 months. Disease flare occurred in 81% of those switched to placebo therapy and 28% who continued on the etanercept therapy during the 4-month period. The median time to the flare was 28 days after being switched to placebo and 116 days with continued etanercept therapy. The results from this phase of the study are summarized in Table 6.

Table 5: Median Improvement in Measures of JRA Disease Activity in Children Treated with Etanercept for 3 Months (n=69):

Parameter	Baseline	Month-3	Improvement
# Active joints	28	13	56%
# Joints with LOM + P/T	10	2	79%
Physician global assessment (0-10)	7	2	60%
Patient global assessment (0-10)	5	2	50%
Health assessment questionnaire (1-4)	1.4	0.9	37%
Erythrocyte sedimentation rate (mm/hr)	35	20	50%
C-reactive protein (mg/dL)	3.5	0.8	60%
Pain B VAS (0-10)	3.6	1.4	63%
Morning stiffness (min)	45	15	75%

LOM = loss of motion  
P/T = pain/tenderness

Table 6: Median Results from the Double-Blind Phase of the Juvenile Rheumatoid Arthritis Study:

Parameter	Placebo (n=26)		Etanercept (n=25)	
	Month-3	Month-7	Month-3	Month-7
# Active joints	8	13	13	7
# Joints with LOM + P/T	17	22	12	9
Physician global assessment (0-10)	1	5	2	2
Patient global assessment (0-10)	1	5	2	3
Health assessment questionnaire (1-4)	0.5	1.2	0.9	0.8
Erythrocyte sedimentation rate (mm/hr)	12	30	15	18
C-reactive protein (mg/dL)	0.3	3	0.2	0.4
Pain B VAS (0-10)	0.3	3.5	1.3	1.5
Morning stiffness (min)	5	38	15	5

LOM = loss of motion  
P/T = pain/tenderness

*Renal Allograft:* Preliminary data from animal models indicate that etanercept is effective in prolonging renal allograft survival alone or in combination with cyclosporine.

*Heart Failure:* The results from a Phase I study of etanercept for the treatment of patients with NYHA Class III heart failure are encouraging. Eighteen patients were treated with intravenous etanercept or placebo. Symptomatology and walk distance of the patients were improved following treatment with etanercept.

*Cachexia:* Preliminary results from animal models indicate that etanercept may be an effective means of preventing cachexia and runting. This effect may be useful in the treatment of patients with cancer, acquired immunodeficiency syndrome and advanced heart failure.

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** Etanercept is contraindicated in patients who are allergic to the drug, other product ingredients (mannitol, sucrose, tromethamine) or benzyl alcohol. Etanercept treatment should be discontinued if a patient develops a serious infection, with or without hypotension, which suggests impending sepsis syndrome.

Etanercept should be discontinued if the child develops a varicella infection or has a significant exposure to varicella virus. In addition, treatment with Varicella Zoster Immune Globulin should be considered if the exposure was significant.

Allergic reactions to etanercept do occur rarely (<0.5%) but no cases of anaphylaxis have been reported.

Antibodies to etanercept have been detected in the sera of 16% of the rheumatoid arthritis patients treated with etanercept. However, none of these antibodies were neutralizing antibodies and did not decrease the drug's effectiveness or cause adverse effects.

Etanercept can be used during pregnancy (Category B) but no studies have been conducted in pregnant women. So the drug should only be used during pregnancy if clearly needed. Use of etanercept during nursing is discouraged since it is unknown if etanercept is excreted in breast milk. The manufacturer recommends that either the nursing or drug be discontinued.

Live vaccines should not be given concurrently with etanercept therapy.

**ADVERSE REACTIONS:** The most common adverse reactions reported with etanercept were injection site reactions (37%). These reactions were classified as mild-to-moderate injection site reactions (erythema, erythema plus discomfort, itching or swelling). The injection site reactions do not occur with

each dose, occur most frequently in the first month of therapy and decrease in frequency with continued therapy. The reaction generally resolved within 3 to 5 days.

Other adverse reactions reported with etanercept therapy have included mild upper respiratory tract symptoms, headache, dizziness, abdomen pain, dyspepsia and rash. See Table 7 for a list of the more frequent adverse effects reported in the product labeling.

Table 7: Incidence of Adverse Reactions with Etanercept Therapy in the Treatment of Rheumatoid Arthritis:

Adverse Effect	Percent of Patients		Events per Patient Year	
	Placebo (n=152)	Etanercept (n=349)	Placebo (40 pt years)	Etanercept (117 pt years)
Injection site reactions	10%	37%	0.62	7.73
Rash	3%	5%	0.12	0.21
Infection	32%	35%	1.86	1.82
Non-upper respiratory infection	32%	38%	1.54	1.5
Upper respiratory infections	16%	29%	0.68	0.82
Respiratory disorder	1%	5%	0.05	0.17
Sinusitis	2%	3%	0.07	0.12
Rhinitis	8%	12%	0.35	0.45
Pharyngitis	5%	7%	0.17	0.24
Cough	3%	6%	0.17	0.18
Headache	13%	17%	0.62	0.68
Dizziness	5%	7%	0.25	0.21
Asthenia	3%	5%	0.1	0.16
Pain, abdomen	3%	5%	0.12	0.17
Dyspepsia	1%	4%	0.05	0.12

Etanercept does not affect immune function. Mild upper respiratory tract symptoms (eg, cough, rhinitis, sinusitis, upper respiratory tract infections, pharyngitis) appeared to occur more frequently in the etanercept group, but were not significantly different than placebo when analyzed over time. However, patients who are TNF1/2 heterozygotes or FcRIII-176F/F homozygotes may be more likely to develop an infection when treated with placebo or etanercept.

Adverse effects resulted in discontinuation of therapy in 4% of the patients treated in the clinical trials. The same percent required the discontinuation of their placebo therapy due to adverse effects in the same studies.

The occurrence of new malignancies during etanercept therapy appears no different than the rate expected in this patient population. While the development of antinuclear antibodies (11% vs 5%) and anti-double stranded DNA antibodies (15% vs 4% using the radioimmunoassay and 3% vs 0% with the Crithidia lucilae assay) are higher in patients treated with etanercept than those receiving a placebo. No patients have shown signs or symptoms or developed lupus-like syndrome or other new autoimmune diseases.

**MONITORING:** The signs and symptoms of rheumatoid arthritis should improve within several weeks to months of starting etanercept therapy. No special laboratory monitoring is required.

It may be beneficial to reassess the patient's ability to reconstitute and administer the product periodically throughout therapy, especially if there appears to be a reduction in drug effectiveness.

**DRUG INTERACTIONS:** No specific drug interaction studies have been conducted with etanercept. However, patients enrolled in the clinical studies were allowed to receive methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics and/or hormone replacement therapy and no adverse effects were associated with the concomitant use of these agents with etanercept.

It is unknown if etanercept will affect the immune response to vaccines, so all scheduled vaccinations should be completed prior to starting etanercept therapy.

**DOSING:** The most effective dose of etanercept used in the treatment of adults is 25 mg subcutaneously twice weekly. The dose of etanercept used in the treatment of juvenile rheumatoid arthritis is 0.4 mg/kg, with a maximum dose of 25 mg subcutaneously twice weekly. Safety in children less than 4 years has not been evaluated.

Some patients will choose to self-administer their etanercept. These patients will need to be taught how to correctly reconstitute the product, prepare the syringe for use, safely inject the drug and dispose of the syringe and needle in the puncture-resistant container. The first preparation and injection should be performed under the supervision of a qualified health care professional.

Preferred subcutaneous injection sites include the thigh, abdomen and upper arm. The injection site should be rotated with each dose. The new injection should be given at least 1 inch from a previously used injection site. If the skin is tender, bruised, red or hard, then that area should be avoided.

**PRODUCT AVAILABILITY:** The New Drug Application for etanercept was submitted to the FDA on 7 May 1998. On 16 September 1998, the Arthritis Advisory Committee recommended it be approved for the treatment of rheumatoid arthritis in patients who have failed to respond to other DMARDs. Etanercept will be marketed by Immunex Corporation and Wyeth-Ayerst Laboratories for all indications except oncology, which will be done by Immunex alone.

Etanercept is a preservative-free, lyophilized powder. It contains mannitol, sucrose and tromethamine. Reconstitution is done with 1 mL of Sterile Bacteriostatic Water for Injection, USP (containing 0.9% benzyl alcohol). The reconstituted solution is clear, colorless with a pH of 7.4.

The product is available in cartons containing 4 dose trays. Each tray contains a 25 mg single-use vial of etanercept, a syringe (1 mL Sterile Bacteriostatic Water for Injection, USP), a plunger and 2 alcohol swabs. These packages must be stored in the refrigerator (2E to 8EC) and prevented from freezing. Once the etanercept is reconstituted, it should be administered as soon as possible, but it can be stored in the vial under refrigeration (2E to 8EC) for up to 6 hours.

Also available are a teaching system for health care professionals and a set of tools for the patient. The health care professional's teaching system includes a videotape on how to prepare and administer the drug, a step-by-step visual guide on preparing and administering etanercept, injection teaching model, demonstration practice kit, mixing station, dosing tablemat, *EnlivenJ* Patient Support Program enrollment brochure and full prescribing information. The dosing system kit for the patient includes a videotape on how to prepare and administer etanercept, a step-by-step visual guide on preparing and administering etanercept, dosing tablemat, mixing station, *EnlivenJ* Patient Support Program enrollment brochure, sharps container and product information. The *EnlivenJ* Patient Support Program is designed to provide support and information to patients starting on etanercept therapy. This program is 6 months long and is free. Patients can enroll in the program by calling 1-888-436-2735.

Cost approximately \$12,600.00 per year for 25mg twice weekly AWP (\$550.00 per 4 x 25mg doses).

**CONCLUSION:** Etanercept is a very useful form of biologic response modifiers for the treatment of patients with active rheumatoid arthritis who have failed to respond to other DMARDs. Like previous therapies, etanercept does not cure the disease. Etanercept is only available for parenteral administration; because it is a large protein, it would be destroyed by gastric acid. Study results show that the drug is capable of decreasing joint pain and swelling, decreasing the sedimentation rate and C-reactive protein, improving the patient's functional ability and decreasing morning stiffness and fatigue.

**ROTAVIRUS VACCINE, LIVE, ORAL, TETRAVALENT - ROTASHIELD™** (Wyeth-Ayerst Laboratories)

**INDICATIONS:** Rotavirus vaccine is indicated in infants for the prevention of gastroenteritis caused by those rotavirus serotypes contained in the vaccine ([G] 1, 2, 3 and 4). The CDC Advisory Committee on Immunization Practices (ACIP) voted to recommend routine use of rotavirus vaccine for all healthy full-term infants.

The recommended dosing schedule for oral immunization is at 2, 4 and 6 months of age. Because infants older than 6 months may have an increased risk of fever subsequent to administration of the first dose of the vaccine, initiation of vaccination after the age of 6 months is not recommended. Administration of any dose is also not recommended in children over 12 months of age due to a lack of safety and efficacy data in that population.

**CLINICAL PHARMACOLOGY:** Rotavirus vaccine is a live, oral, tetravalent vaccine containing four live viruses: an attenuated rhesus monkey rotavirus strain (VP7 immunologically similar to human serotype G3) and three rhesus-human reassortant viruses (expressing human VP7 serotypes G1, G2 and G4). Rhesus-human reassortant rotavirus strains contain a single human rotavirus gene that specifies for the neutralization of viral protein 7 (VP7) and 10 remaining genes from the parent rotavirus strain. The viruses are grown in a fetal rhesus diploid cell line; following harvest, residual cellular debris is removed by filtration. Sucrose, monosodium glutamate, potassium monophosphate and potassium diphosphate are added to stabilize the rotavirus. Fetal bovine serum, neomycin sulfate and amphotericin B are present during cell culture growth. These agents are removed before virus infection and are present in the final preparation at a concentration of less than 1 mcg per dose.

Group A rotaviruses are wheel-shaped RNA viruses. They are the four serotypes of rotavirus that cause the majority of rotavirus disease in the U.S. Rotavirus is the most important cause of severe gastroenteritis in infants and young children in developed and developing countries. In the U.S. each year, it is estimated to cause rotaviral gastroenteritis requiring treatment in 411,000 infants under 1 year of age and 1 million children between 1 and 2 years of age. Approximately half of these children develop severe diarrhea. It has been estimated to cause 600,000 to 870,000 deaths annually in developing countries and several hundred deaths each year in the U.S. Children 3 to 24 months of age have the highest rates of severe diarrhea and hospitalization. Rotavirus causes about 5% of diarrheal illness, but nearly 40% of the severe dehydrating illness. In the U.S., one in eight of all infants require medical treatment for rotaviral gastroenteritis and 1 in 50 is hospitalized. In the U.S., rotavirus emerges in the southwest in November and spreads north and east, peaking in the northeast in March and April. Annual direct medical costs from rotavirus disease are estimated at \$270 to 450 million and annual total societal costs (including lost parental time from work) are estimated at \$1 billion.

Primarily the fecal-oral route transmits rotavirus. It is highly infectious and hygiene measures have been largely ineffective in controlling infection. Ingested viral particles infect the cells of the villi of the small intestine. The incubation period is 1 to 2 days which is then followed by the development of acute watery diarrhea in copious amounts in some patients and may be accompanied by vomiting. The rotavirus vaccine was developed to prevent severe diarrhea associated with the infection in infants and young children and not to eliminate the rotavirus. The mechanism of immune response to the vaccine is not well understood. The vaccine virus

generates IgG antibodies that neutralize the serotype 3 parent rotavirus strain as well as human rotavirus serotypes 1, 2, 3 and 4. IgA antibody is also induced, suggesting a local immune response. Natural rotavirus infection results in partial protection against subsequent illness, with reinfection resulting in mild or asymptomatic disease.<sup>1,9,10</sup> Similar effects are anticipated with the vaccine.

The higher postvaccination IgA titers seen in 16- to 24-week-old infants versus younger infants following dose administration is probably due to the lower levels of preexisting maternal antibodies in the older infants. Maternal antibodies are present at birth and are acquired through breast milk, which may lower the young infants response to the vaccine. However, with a 3-dose series of the  $4 \times 10^5$  pfu dose vaccine administered at 2, 4 and 6 months, seroconversion has occurred in more than 90% of infants in U.S. studies. Much lower seroconversion rates are observed in infants who received the first dose of a 2-dose series as neonates due to the interference of maternal antibodies. Lower conversion rates are observed with lower titer tetravalent vaccine and vaccines specific to one particular serotype. Although administration of a tetravalent vaccine containing  $4 \times 10^5$  pfu produces a greater rate of seroconversion than the  $4 \times 10^4$  dose, a higher dose ( $4 \times 10^6$  pfu) offered no advantage over the lower-titer product.

**PHARMACOKINETICS:** The vaccine virus replicates in the intestine and is shed in the stool. Low-level transmission has been detected; however, vaccine virus does not appear to cause disease.

**EFFICACY:** Overall, in four placebo controlled trials, three doses of the vaccine were approximately 50% effective against any diarrhea caused by rotavirus and 70% to 95% effective against severe rotavirus diarrhea.

The rotavirus vaccine was administered to 10,816 subjects in clinical trials prior to the vaccines approval. Three placebo controlled trials in which 2,014 infants received three doses of the vaccine by 33 weeks of age and which provided the basis for vaccine approval, are summarized in the package literature. In each of these studies, vaccine recipients experienced fewer episodes of rotaviral gastroenteritis, fewer episodes of severe rotaviral gastroenteritis and fewer episodes of rotaviral gastroenteritis requiring medical attention. In addition, immunization was associated with a reduction in diarrhea caused by rotaviral gastroenteritis by approximately 1 day compared to placebo and a reduction in vomiting caused by rotaviral gastroenteritis by approximately 1 day compared with placebo.

Trial 1 was a multicenter trial evaluating the tetravalent rotavirus vaccine compared to placebo in 783 healthy U.S. infants. Subjects received three doses of either placebo or the tetravalent rotavirus vaccine at approximately 2, 4 and 6 months of age prior to the start of the rotavirus season and completed one full season of surveillance. Another group of infants enrolled in this study received a monovalent rotavirus vaccine (serotype 1) which was less effective than the tetravalent vaccine. Vaccination prevented 49% of rotavirus episodes, 80% of severe rotavirus episodes and 100% of dehydrating rotavirus episodes and produced a reduction in episodes of gastroenteritis of all causes and an 82% reduction in all cases of dehydrating diarrhea. Rotaviral gastroenteritis occurred in 13% of vaccine-treated infants compared to 25% of placebo-treated infants. Vaccinated infants in this study who did develop rotaviral gastroenteritis experienced less severe illness than the infants who received the placebo. Severe illness occurred in 2% of treated infants compared to 9% of placebo recipients. Medical intervention for rotaviral illness was necessary in 4% of vaccine recipients compared to

15% of placebo recipients. Dehydration caused by rotaviral gastroenteritis occurred in none of the vaccine recipients compared with 3% of the placebo recipients. Seroconversion for rotavirus IgA occurred in 92% of vaccine recipients and 4% of placebo recipients.

Trial 2 was a multicenter study evaluating the tetravalent rotavirus vaccine compared to placebo in 695 healthy Native American infants. Another group of infants enrolled in this study received a monovalent rotavirus vaccine (serotype 1) which was less effective than the tetravalent vaccine. Subjects received three doses of either placebo or the tetravalent rotavirus vaccine at approximately 2, 4 and 6 months of age prior to the start of the rotavirus season and completed one full season of surveillance. Seroconversion for rotavirus IgA occurred in 93% of the vaccine recipients and 19% of the placebo recipients. Vaccine efficacy was 50% for all rotavirus gastroenteritis and 69% for severe rotavirus gastroenteritis after 1 year. Efficacy decreased during the second year, but still favored the tetravalent vaccine (-3% for all serotypes and 44% severe gastroenteritis) over the monovalent vaccine and placebo.<sup>13</sup> Rotavirus gastroenteritis occurred in 11% of vaccine-treated infants compared to 23% of placebo-treated infants. Severe illness occurred in 2% of treated infants compared to 8% of placebo infants. Medical intervention for rotaviral illness was necessary in 5% of vaccine recipients compared to 16% of placebo recipients. Dehydration caused by rotavirus gastroenteritis occurred in 1% of the vaccine recipients and 3% of the placebo recipients.

Trial 3 was a multicenter study performed in 2,273 healthy infants in Finland. Subjects received three doses of either placebo or rotavirus vaccine at approximately 2, 3 and 5 months of age given throughout the year, and completed at least one full season of surveillance. During the first year of surveillance, rotaviral gastroenteritis occurred in 1% of vaccine-treated infants compared to 9% of placebo-treated infants. Severe illness occurred in less than 1% of vaccine treated infants compared to 4% of placebo recipients. Over 2 years of surveillance, rotaviral gastroenteritis occurred in 5% of vaccine-treated infants compared to 15% of placebo-treated infants. Severe illness occurred in 1% of vaccine-treated infants compared to 8% of placebo-treated infants. Medical intervention for rotaviral illness was necessary in 1% of vaccine recipients compared to 7% of placebo recipients. Dehydration caused by rotaviral gastroenteritis occurred in less than 1% of the vaccine recipients compared with 3% of the placebo recipients. Overall, vaccination prevented 68% of rotaviral episodes and 91% of severe rotaviral episodes. Vaccinated infants in this study who did develop rotaviral gastroenteritis experienced less severe illness than the infants who received placebo.

The vaccine was also evaluated in a double-blind, placebo controlled study performed in 2,037 infants in Venezuela who received three doses of either placebo or rotavirus vaccine at approximately 2, 3 and 4 months of age and completed approximately 19 to 20 months of surveillance. Vaccination prevented 48% of rotaviral episodes, 88% of severe rotaviral episodes and 75% of dehydrating episodes and also reduced hospital admissions by 70%. Seroconversion for rotavirus IgA occurred in 80% of vaccine recipients.

The tetravalent vaccine at a lower dose of  $4 \times 10^4$  plaque-forming units prevented 57% of rotaviral gastroenteritis and 82% of severe rotaviral gastroenteritis. It also produced a 78% reduction in medical visits for rotaviral gastroenteritis in a large US study enrolling 1,006 infants administered the tetravalent vaccine, a monovalent (serotype 1) vaccine or placebo.<sup>22</sup> Tetravalent vaccine at a dose of  $4 \times 10^4$  plaque-forming units administered at 2, 3 and 4 months in a placebo controlled study performed in 638 infants in Lima, Peru, produced

seroconversion in 75% of infants and provided moderate protection against severe rotaviral gastroenteritis but did not decrease the incidence of rotaviral diarrhea overall.<sup>23</sup> The tetravalent vaccine at a dose of  $4 \times 10^4$  plaque-forming units administered at 2, 4 and 6 months of age produced seroconversion for rotavirus IgA in 67% of vaccinated infants compared to 16% of placebo recipients in a study performed in 187 infants in Thailand.

Several cost-effectiveness analyses were performed to estimate the economic impact of a national rotavirus immunization program in the U.S. It was estimated in one assessment that vaccination using the tetravalent rotavirus vaccine administered at 2, 4 and 6 months of age as part of routine childhood immunizations in the U.S. would prevent 1.08 million cases of diarrhea, avoiding 34,000 hospitalizations, 95,000 emergency department visits and 227,000 physician visits in the first 5 years of life. At \$20 per dose (less than the vaccines estimated market cost), the immunization program would cost \$289 million and realize a net loss of \$107 million to the health care system; \$103 per case prevented. The program would provide net savings of \$296 million to society. The break-even price per dose would be \$9 for the health care system and \$51 for the societal perspective. Another analysis suggested that routine immunization with the rotavirus vaccine in the U.S., assuming an efficacy rate of 50% and a \$30 cost per dose, would cost \$243 million per year, but would yield a net savings of \$79 million from the perspective of the health care system and \$466 million from the perspective of society based on prevention of more than 1 million cases of rotaviral diarrhea, 58,000 hospitalizations and 82 deaths each year. Another analysis suggested a break-even cost of immunization of \$11 per infant for the tetravalent vaccine. It appears unlikely based on the estimated cost of the vaccine per dose of \$38 that vaccination will prove cost-effective from the perspective of the health care system, but it may prove cost-effective from the societal perspective.

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** Rotavirus vaccine is for oral administration only and should not be given parenterally. The vaccine is contraindicated in patients with hypersensitivity to any component of the vaccine, such as aminoglycoside antibiotics, monosodium glutamate or amphotericin B, or ongoing diarrhea or vomiting. It is also contraindicated in patients with known or suspected immune deficiency diseases and conditions such as combined immunodeficiency, hypogammaglobulinemia, agammaglobulinemia, human immunodeficiency virus infection, thymic abnormalities, malignancy, leukemia, lymphoma or advanced debilitating conditions. It is also contraindicated in patients who may be immunosuppressed or have an altered or compromised immune status, such as those who are being treated with systemic corticosteroids, alkylating drugs, antimetabolites, radiation or other immunosuppressive therapies. Corticosteroid therapy does not contraindicate vaccination if it is short term (eg, less than 2 weeks); low-to-moderate dose; long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy) or administered topically, by aerosol or intra-articular, bursal or tendon injection.

The vaccine virus may be transmitted from vaccine recipients to nonrecipients. It should not be administered to immunosuppressed infants. Close association between immunocompromised individuals and vaccine recipients should be avoided, whenever possible, for up to 4 weeks. For infants living in a household with an immunosuppressed family member or where contact with high-risk individuals is unavoidable, the potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus.

The vaccine should be administered with caution to patients with a history of latex sensitivity, as the packaging contains dry natural rubber.

Routine use in premature infants is not recommended at this time due to a lack of data in premature infants less than 37-weeks gestation, a lack of information on the risk of rotavirus infection in premature infants and a lack of information on the incidence of adverse reactions in this population. The potential benefits and risks of vaccination should be considered individually before administering the rotavirus vaccine to a premature infant.

It is not recommended for use in adults.

**ADVERSE REACTIONS:** In placebo controlled trials, fever, decreased appetite, abdominal cramping, irritability and decreased activity were observed more frequently in vaccinated infants than in placebo recipients in the 5 days after administration. Reactions occur more frequently after the first dose than after subsequent doses.<sup>40</sup> Fever has typically appeared 3 to 5 days after vaccine administration.<sup>4,40</sup> The rate of diarrhea is not increased.

**DRUG INTERACTIONS:** Coadministration of the rotavirus vaccine with oral poliovirus vaccine (OPV), inactivated parenteral poliovirus vaccine (IPV), diphtheria-tetanus-whole-cell pertussis (DTP), *Haemophilus influenzae* type b (Hib), and hepatitis B vaccines does not interfere with the immune response to any of these vaccines.

Although breast milk, which may contain maternal antibodies to rotavirus, can interfere with the immune response to the rotavirus vaccine, the effect appears to be small and is overcome by administration of three doses of the vaccine. The vaccine can be administered to infants who are breast fed exclusively or partly, and a delay in administration following breast feeding is not recommended.

**DOSING:** Rotavirus vaccine is administered orally as three 2.5 mL doses. The recommended dosing schedule is at 2, 4 and 6 months of age. The first dose may be administered as early as 6 weeks of age, with subsequent doses at least 3 weeks apart. In clinical trials, infants have received the third dose at up to 33 weeks of age with no increased adverse reactions. Because infants older than 6 months of age may have an increased risk of fever subsequent to administration of the first dose of the vaccine, initiation of vaccination after the age of 6 months is not recommended. The vaccine should also not be given to children over 12 months of age.

There are no restrictions on consumption of food or liquid, including breast milk, before or after vaccination. Repeat dosing is not indicated if an infant should regurgitate vaccine.

Rotavirus vaccine can be administered concomitantly with OPV, DTP and Hib. Studies evaluating administration with other childhood vaccines are currently ongoing.

**PRODUCT AVAILABILITY:** The rotavirus vaccine received FDA approval in August 1998. It is available as a pink lyophilized preparation that appears yellow-orange to purple when reconstituted and may contain a fine precipitate. It is reconstituted with an irradiated sterile citrate-bicarbonate diluent containing 9.6 mg/mL of citric acid and 25.6 mg/mL of sodium bicarbonate. The buffering action of the diluent neutralizes stomach acidity and protects the

acid-labile rotaviruses from degradation. Each 2.5 mL dose is formulated to contain equal quantities of each of the four viral serotypes with a total viral content of  $4 \times 10^5$  pfu. The vaccine contains no preservatives. The lyophilized vaccine and diluent may be stored at room temperature or under refrigeration.

Each dose is provided in a 5 mL screw-cap vial containing the lyophilized vaccine and a Dispette assembly containing the buffer diluent. To reconstitute the vaccine, the contents of the Dispette are squeezed into the vial containing the vaccine. Resuspension is instantaneous. The contents are drawn back into the Dispette. The Dispette is placed into the child's mouth and the contents slowly squeezed out.

Ideally the vaccine should be administered immediately after reconstitution. The Dispette containing the reconstituted solution can be recapped and stored for up to 60 minutes at room temperature or up to 4 hours under refrigeration.

**CONCLUSION:** The rotavirus vaccine reduces the incidence of severe rotaviral gastroenteritis. It will be incorporated into the routine childhood immunization schedule and should be offered to all healthy full-term infants, unless contraindicated. Use should also be considered on a case by case basis in premature infants.

FIGURE 1. Recommended childhood immunization schedule\* — United States, January–December 1999

Vaccine	Age										
	Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	4–6 yrs	11–12 yrs	14–16 yrs
Hepatitis B <sup>†</sup>	Hep B		Hep B		Hep B						
Diphtheria and tetanus toxoids and pertussis			DTaP	DTaP	DTaP		DTaP		DTaP	Td	
<i>H. influenzae</i> type b <sup>†</sup>		Hib	Hib	Hib	Hib						
Poliovirus**		IPV	IPV	Polio					Polio		
Rotavirus		Rv	Rv	Rv							
Measles-mumps-rubella <sup>††</sup>					MMR			MMR	MMR		
Varicella <sup>†††</sup>						Var				Var	

-  Range of Acceptable Ages for vaccination
-  Vaccines to be Assessed and Administered if Necessary
-  Incorporation of this new vaccine into clinical practice may require additional time and resources from health-care providers.

\* This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines. Any dose not given at the recommended age should be given as a "catch-up" vaccination at any subsequent visit when indicated and feasible. Combination vaccines may be used whenever any components of the combination are indicated and its other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

<sup>†</sup> Infants born to hepatitis B surface antigen (HBsAg)-negative mothers should receive the second dose of hepatitis B (Hep B) vaccine at least 1 month after the first dose. The third dose should be administered at least 4 months after the first dose and at least 2 months after the second dose, but not before age 6 months. Infants born to HBsAg-positive mothers should receive Hep B vaccine and 0.5 mL hepatitis B immune globulin (HBIG) within 12 hours of birth at separate injection sites. The second dose is recommended at age 1–2 months and the third dose at age 6 months. Infants born to mothers whose HBsAg status is unknown should receive Hep B vaccine within 12 hours of birth. Maternal blood should be drawn at the time of delivery to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). All children and adolescents (through age 18 years) who have not been vaccinated against hepatitis B may begin the series during any visit. Special efforts should be made to vaccinate children who were born in or whose parents were born in areas of the world where hepatitis B virus infection is moderately or highly endemic.

<sup>††</sup> Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) is the preferred vaccine for all doses in the vaccination series, including completion of the series in children who have received one or more doses of whole-cell diphtheria and tetanus toxoids and pertussis vaccine (DTP). Whole-cell DTP is an acceptable alternative to DTaP. The fourth dose (DTP or DTaP) may be administered as early as age 12 months, provided 6 months have elapsed since the third dose and if the child is unlikely to return at age 15–18 months. Tetanus and diphtheria toxoids (Td) is recommended at age 11–12 years if at least 5 years have elapsed since the last dose of DTP, DTaP, or DT. Subsequent routine Td boosters are recommended every 10 years.

<sup>†††</sup> Three *Haemophilus influenzae* type b (Hib) conjugate vaccines are licensed for infant use. If Hib conjugate vaccine (PRP-OMP) (PedvaxHIB<sup>®</sup> or ComVax<sup>®</sup> [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required. Because clinical studies in infants have demonstrated that using some combination products may induce a lower immune response to the Hib vaccine component, DTaP/Hib combination products should not be used for primary vaccination in infants at ages 2, 4, or 6 months unless approved by the Food and Drug Administration for these ages.

\*\* Two poliovirus vaccines are licensed in the United States: inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV). The ACIP, AAP and AAP recommend that the first two doses of poliovirus vaccine should be IPV. The ACIP continues to recommend a sequential schedule of two doses of IPV administered at ages 2 and 4 months followed by two doses of OPV at age 12–18 months and age 4–6 years. Use of IPV for all doses also is acceptable and is recommended for immunocompromised persons and their household contacts. OPV is no longer recommended for the first two doses of the schedule and is acceptable only for special circumstances (e.g., children of parents who do not accept the recommended number of injections, late initiation of vaccination that would require an unacceptable number of injections, and imminent travel to areas where poliomyelitis is endemic. OPV remains the vaccine of choice for mass vaccination campaigns to control outbreaks of wild poliovirus.

<sup>††††</sup> The first dose of Rv vaccine should not be administered before age 6 weeks, and the minimum interval between doses is 3 weeks. The Rv vaccine series should not be initiated at age 7 months, and all doses should be completed by the first birthday. The AAP opinion is that the decision to use rotavirus (Rv) vaccine should be made by the parent or guardian in consultation with the physician or other health-care provider.

<sup>†††††</sup> The second dose of measles, mumps, and rubella vaccine (MMR) is recommended routinely at age 4–6 years but may be administered during any visit provided at least 4 weeks have elapsed since receipt of the first dose and that both doses are administered beginning at or after age 12 months. Those who have not previously received the second dose should complete the schedule no later than the routine visit to a health-care provider at age 11–12 years.

<sup>††††††</sup> Varicella (Var) vaccine is recommended at any visit on or after the first birthday for susceptible children (i.e., those who lack a reliable history of chickenpox [as judged by a health-care provider] and who have not been vaccinated). Susceptible persons aged ≥13 years should receive two doses given at least 4 weeks apart.

Use of trade names and commercial sources is for identification only and does not imply endorsement by CDC or the U.S. Department of Health and Human Services.

Source: Advisory Committee on Immunization Practices (ACIP), American Academy of Family Physicians (AAFP), and American Academy of Pediatrics (AAP).

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## LYMERix™ (SmithKline Beecham)-LYME DISEASE VACCINE (Recombinant OspA)

**INDICATIONS:** LYMERix™ is indicated for active immunization against Lyme disease in individuals 15 to 70 years of age, including people who have been infected with Lyme disease. A previous infection may not confer protective immunity; therefore, people with a history of Lyme disease may also benefit from the vaccine.

Those most at risk for acquiring Lyme disease, and therefore those who are the best candidates for the vaccine, are people who live or work in *Borrelia burgdorferi*-infected, tick-infested grassy or wooded areas, as well as those who plan to travel or pursue recreational activities frequently or over prolonged periods in such areas. Most cases of Lyme disease in the United States appear to be acquired in the peri-residential environment, through routine activities of property maintenance, recreation and/or exercise of pets. For those who live in areas where Lyme disease is not endemic or who travel to areas where the disease is endemic, but are not exposed to tick habitats, vaccination is not likely to be beneficial.

Because the vaccine is less than 100% effective and because it does not reduce the risk of other tick-borne diseases, vaccination should not be regarded as a substitute for other preventative measures. In addition to vaccination, people can further reduce their risk of acquiring Lyme disease by avoiding tick habitats, wearing long-sleeved shirts, wearing long pants rather than shorts, tucking pants into socks, treating clothing with tick repellent (permethrin), applying DEET containing repellants to exposed skin (except hands and face), checking for and promptly removing attached ticks and employing community measures to reduce tick abundance.

**CLINICAL PHARMACOLOGY:** Lyme disease is a vector-borne disease caused by the flagellated bacterial spirochete *Borrelia burgdorferi*, which is transmitted from small animal reservoirs to humans by *Ixodes* ticks. All cases of Lyme disease in North America are caused by *B. burgdorferi sensu stricto*. In Europe, Lyme disease is caused by *Borrelia garinii*, *Borrelia afzelii* and *B. burgdorferi*.

The life cycle of *B. burgdorferi* is dependent upon its transmission between an insect vector, the *Ixodes* tick, and a reservoir host, usually the white-footed mouse. *Ixodes* ticks have four developmental stages: egg, larva, nymph and adult. They have a 2-year life cycle. Each of the three motile stages feeds only once prior to molting to the next stage. A blood meal is required for the larval and nymphal stages. In the adult stage, only the female feeds on blood, using the blood meal in the production of eggs. Tick larvae usually feed in the late summer and acquire *B. burgdorferi* from an infected animal host. Nymphal ticks feed in the late spring and summer and serve as the most common source of human infection. Adult ticks feed in the fall, winter and early spring, with the white-tailed deer being the preferred host. Although the prevalence of spirochetes in nymphs (20% to 25%) is approximately half that found in adults, nymphs are responsible for almost 90% of Lyme disease cases due to their smaller size, greater abundance and the timing of their peak feeding activity which coincides with peak human outdoor activity. Adult ticks can also transmit *B. burgdorferi* to humans, and transmission can occur year round. Both deer and rodent hosts are generally necessary to maintain the enzootic cycle of *B. burgdorferi*.

The geographic distribution and abundance of tick species capable of transmitting *B. burgdorferi* to humans determine the regional risk of Lyme disease. Lyme disease is the most commonly diagnosed vector-borne disease in the United States, with over 103,000 cases reported to the CDC from 1982 to 1997. In the United States, 16,461 cases were reported to the CDC in 1996 and 12,801 cases were reported in 1997. Although most cases have been in the Northeast, upper Midwest and Pacific coastal areas, infections have been reported in 48 states and the District of Columbia. The incidence varies from state to state and even within states at the county level. The highest number of cases occur in children 2 to 15 years of age and adults 30 to 55 years of age. Although Lyme disease has been reported worldwide, it is most prevalent in the United States.

Lyme disease is a multisystem disease. The early stage is usually characterized by a rash and may be accompanied by fever, fatigue, myalgias, arthralgias, headache, sore throat and stiff neck. The rash (erythema migrans) is a characteristic expanding red lesion, often with partial central clearing, that occurs at the site of the tick bite. To fit CDC criteria for Lyme disease, the rash must exceed 5 cm in diameter,

show expansion and persist for more than 1 week. The lesion generally progresses at a rate of about 1 cm/day to a final diameter of 10 to 30 cm and persists for 2 to 3 weeks. A tick bite or central punctum is often apparent. Erythema migrans is the presenting symptom in 60% to 80% of patients. Early disseminated manifestations, which generally occur 1 to 4 months after the tick bite, include secondary skin lesions, neurologic involvement (meningitis, facial palsy, other cranial neuritides, radiculoneuritis), cardiac involvement (atrioventricular block, myocarditis) and musculoskeletal symptoms (migratory pain in joints and surrounding soft tissue).

Late-stage disease occurs months to years after the initial infection and may be manifested as chronic arthritis, chronic neurologic abnormalities or acrodermatitis chronica atrophicans. Damage occurring in the late state may be irreversible. Late-stage disease results from early disease that is either unrecognized or fails to respond to therapy, or from asymptomatic infection.

If serologic diagnosis is required, a screening test should be performed first by either enzyme-linked immunosorbent assay (ELISA) or indirect fluorescent antibody assay. If results are positive or equivocal, Western immunoblot testing should be performed. Serologic testing should be considered positive only if both ELISA and Western blot are positive. Vaccination with the Lyme disease vaccine might induce a false-positive ELISA result for *B. burgdorferi* infection. Anti-OspA antibodies can be detected by ELISA for *B. burgdorferi*. Because vaccination may result in a positive IgG ELISA in the absence of infection, Western blot testing should be performed if the ELISA is positive or equivocal in vaccinated individuals being evaluated for Lyme disease.

All stages of Lyme disease are treated with antibiotic therapy. Two to three weeks of oral therapy are generally recommended in early disease. The preferred antibiotics are doxycycline, amoxicillin or cefuroxime axetil. Two to four weeks of intravenous therapy are recommended in neurologic disease. Agents used in the intravenous therapy of Lyme disease include ceftriaxone, cefotaxime and penicillin.

The SmithKline Beecham Lyme disease vaccine is a noninfectious recombinant vaccine containing lipoprotein OspA, an outer surface protein of *B. burgdorferi sensu stricto* ZS7, as expressed by *Escherichia coli*. Kanamycin, an antifoaming agent containing silicon and yeast extract are used in the manufacturing process, however, the kanamycin and silicon are removed to levels below detection. The vaccine is adsorbed onto aluminum hydroxide. Although many types of Lyme disease vaccines have been studied, the lipidated or lipoprotein OspA vaccines have the greatest activity compared to non-lipidated forms and products formed by fusion with proteins from the influenza virus.

*B. burgdorferi* expresses OspA while residing in the midgut of the infected tick, but is down-regulated after tick attachment and is usually undetectable or absent when *B. burgdorferi* is inoculated into the human host. After nymphal tick attachment, spirochete transmission requires approximately 48 hours during which time *B. burgdorferi* multiply and cross the gut epithelial barrier into the lymph, disseminate into the salivary glands and infect the host via tick saliva. It has been proposed that when infected ticks bite humans who have been vaccinated with the lipoprotein OspA Lyme disease vaccine, the vaccine-induced antibodies are taken up by the tick and interact with the *B. burgdorferi* in the midgut of the tick, blocking spirochetal growth and salivary gland invasion and thereby preventing transmission of the organism from the vector to the host. Such activity has been demonstrated in ticks allowed to feed on vaccinated mice. Activity is only evident when OspA antibodies are present at the time of the initial tick attachment, since OspA disappears from *B. burgdorferi* within 24 hours of attachment. Concerns have been raised that this mechanism may allow for selection of spirochetes that are not susceptible to the actions of the antibodies. Spirochetes with a low surface density of OspA molecules and enhanced motility or ability to penetrate the tick midgut wall could potentially escape antibody-dependent killing. In one animal study, transient low level infection was observed that was believed to be due to transfer of a small number of spirochetes to the host that were of insufficient number to produce a full blown infection, but were of sufficient quantity to be detectable for a period of time.

Seroconversion following vaccination, with IgG OspA antibody titers >20 EL.U./mL or a LA-2 equivalent antibody titer >100 ng/mL, occurred in 97% to 100% of patients following three doses of the SmithKline Beecham vaccine administered in a 0-, 1- and 12-month schedule. Table 1 summarizes the rates of seroconversion from the primary efficacy study. Similar results were obtained with the lipoprotein OspA

vaccine in a study examining the immune response to vaccination with the lipoprotein OspA vaccine and two other vaccine formulations administered in a three-dose (0, 1, and 2 month) schedule. Four months following the third dose of the lipoprotein OspA vaccine, 100% of the patients remained seropositive. Administration of the vaccine on a 0-, 1-, 2-, and 12-month schedule in another study also demonstrated titers after the third dose comparable to those reported after the third dose of the vaccine administered on a 0-, 1- and 12-month schedule. Greater protection would be expected to be achieved more quickly with such a schedule. Results have also been presented in abstract from a study evaluating the Lyme disease vaccine administered on a schedule of 0, 1 and 6 months compared to the schedule of 0, 1 and 12 months in 800 subjects. Immune responses were equivalent in terms of geometric mean antibody titer and distribution of individual titers. Greater than 97% seroconversion was also reported in a dose-finding study, with immunogenicity correlating with the vaccine dose. High rates of seroconversion (99% to 100%) after two doses were also reported in a study evaluating the vaccine at doses of 15 mcg and 30 mcg administered on a 0-, 1- and 2-month schedule in children aged 5 to 15 years. The third dose increased the geometric mean titers 2.5 times. The duration of immunity following a complete schedule of immunization has not been established.

Table 1: Seroconversion Rates with the SKB Lyme Disease Vaccine:

Antibody	Sampling Time	Seropositivit y
Total IgG Anti-OspA	1 mo. after dose-2	99%
	Pre-dose-3	83%
	1 mo. after dose-3	100%
	7 mos. after dose-3	98%
LA-2 Equivalent	1 mo. after dose-2	96%
	Pre-dose-3	58%
	1 mo. after dose-3	99%
	7 mos. after dose-3	97%

In 30 subjects with a history of Lyme disease, administration of the Lyme disease vaccine at doses of 3 mcg, 10 mcg and 30 mcg administered at 0, 1 and 2 months was also assessed. Prior to vaccination, 20% of the subjects had low-titer antibodies to OpsA. After completion of the vaccination schedule, the geometric mean antibody titer to OspA increased greater than 10-fold. The highest titers were observed in the subjects receiving the 30 mcg dose, although high titers were also observed in some subjects who received the 3 mcg and 10 mcg doses. The results of this study confirmed that subjects with a history of Lyme disease do develop high titers after Lyme disease vaccination and therefore are no less likely to respond to the vaccine.

A purified OspA lipoprotein Lyme disease vaccine is also under development by Pasteur Merieux Connaught. Antibody responses to adjuvant and nonadjuvant forms of the Pasteur Merieux Connaught vaccine were also assessed. IgG anti-OspA geometric mean titers increased approximately five-fold over baseline levels by 3 weeks after the first dose of both forms of the vaccine. Further increases were observed after a second dose administered 4 weeks after the first, reaching levels approximately 40-fold over baseline levels by 2 weeks after the second dose. Titers declined over the subsequent 4 months, but remained at levels similar to those observed prior to the administration of the second dose. A third dose produced an approximate 10-fold increase in titers. The seroconversion rate was 92%. In another study with the nonadjuvant form of the vaccine, 9 of 11 (81%) recipients of two 30 mcg doses administered 1 month apart still had measurable OspA antibody titers 6 months after the first dose. Peak titers were observed 2 months after the second dose. Despite high antibody titers, correlation was not observed with borreliacidal activity that waned rapidly and was detectable in only one patient at 6 months.

Not all isolates of *B. burgdorferi* express OspA to the same extent, although most isolates in the United States are fairly homogenous. Isolates from Europe are more diverse. Some strains express little or no OspA. The OspA vaccine will not protect against isolates that do not express OspA. In an animal study,

a monovalent ZS7 OspA vaccine did not protect against infection with *B. garinii* and *B. afzelii*. Several sources have suggested a multivalent vaccine may be necessary in Europe, while the monovalent vaccine should be effective in the United States.

**EFFICACY:** The primary study demonstrating the efficacy of the commercially available Lyme disease vaccine enrolled 10,936 subjects 15 to 70 years of age residing in endemic areas of the United States, primarily in the Northeast. Vaccine was administered to 5,469 subjects and placebo to 5,467 subjects. Subjects received three doses of placebo or 30 mcg purified OspA lipoprotein vaccine at months 0, 1 and 12 and were observed for 20 months after the first injection (January 1995 through November 1996). Vaccine efficacy against definite Lyme disease was 78% after three doses of the vaccine (95% CI: 59% to 88%; 13 cases among 4,765 vaccine recipients and 58 cases among 4,784 placebo recipients). Definite disease was defined as clinical manifestations with laboratory confirmation. After two doses, vaccine efficacy against definite disease was 50% (95% CI: 14% to 71%; 20 cases among 5,148 vaccine recipients and 40 cases among 5,166 placebo recipients). Vaccine efficacy against asymptomatic disease, defined as IgG Western blot seroconversion in the absence of recognizable symptoms, was 100% after three doses (95% CI: 30% to 100%; zero cases among 4,765 vaccine recipients and 13 cases among 4,784 placebo recipients) and 83% after two doses (95% CI: 25% to 96%; two cases among 5,148 vaccine recipients and 12 cases among 5,166 placebo recipients).<sup>1,20</sup> In a dose-ranging study with the SmithKline Beecham vaccine, 350 subjects living in a region of New England where Lyme disease is highly endemic received three vaccine doses at monthly intervals. Anti-OspA antibodies were detected in more than 97% of subjects. Vaccine efficacy against laboratory-confirmed clinical Lyme disease was 100%.

A study is currently underway evaluating the SmithKline Beecham vaccine in children.

Another large study evaluated a similar Lyme disease vaccine manufactured by Pasteur Merieux Connaught. This vaccine also consists of purified OspA lipoprotein, but differs from the SmithKline Beecham vaccine in that it is not adsorbed to aluminum hydroxide. It was evaluated in a double-blind trial enrolling 10,305 subjects 18 years of age or older living in areas of the United States where Lyme disease is endemic. Subjects received two doses of either 30 mcg of the OspA vaccine or placebo. The second injection was given approximately one month after the first. At the request of the FDA, a third dose was administered approximately 12 months after the first injection to 7,515 subjects. Vaccine was administered to 5,149 subjects and placebo to 5,156 subjects. Three doses were received by 3,745 subjects in the vaccine group and 3,770 subjects in the placebo group. Vaccine efficacy against definite Lyme disease was 68% in the first year of the study (95% CI: 36% to 85%; 12 cases among 5,156 vaccine recipients and 37 cases among 5,149 placebo recipients). Definite disease was defined as clinical manifestations with laboratory confirmation. Vaccine efficacy against definite disease was 92% in the second year of the study among patients who received the 12-month booster dose (95% CI: 69% to 97%; two cases among 3,745 vaccine recipients and 26 cases among 3,770 placebo recipients).

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** The Lyme disease vaccine is contraindicated in people with known hypersensitivity to any component of the vaccine. Packaging for the prefilled syringes contains natural rubber; the vial does not. A moderate or severe febrile illness is sufficient reason to postpone vaccination; however, minor illnesses are not a contraindication. Administration is not recommended in patients with treatment-resistant Lyme arthritis (antibiotic refractory), as immune reactivity to OspA of *B. burgdorferi* has been observed in this population.

The vaccine will not prevent disease in those with unrecognized infection at the time of vaccination and will not provide protection against other tick-borne diseases. The expected immune response may not be obtained in immunosuppressed persons or persons receiving immunosuppressive therapy. Vaccination may be postponed until 3 months after immunosuppressive therapy.

The Lyme disease vaccine is categorized in Pregnancy Category C. Animal reproductive studies have not been performed. It is not known if the Lyme disease vaccine is excreted in breast milk.

Safety and efficacy have not been established in children less than 15 years of age.

**ADVERSE REACTIONS:** The most frequently reported adverse effects, occurring with a greater frequency in vaccine recipients than placebo recipients in clinical trials, have included injection site pain, injection site reactions, local muscle pain, chills/rigors, fever, influenza-like symptoms, fatigue, myalgia and rash. Local symptoms primarily consisted of redness, soreness and swelling.

**DRUG INTERACTIONS:** No data are available on the immune response to the Lyme disease vaccine when administered concurrently with other vaccines. Since the vaccine is administered intramuscularly, it should not be given to patients receiving anticoagulant therapy unless the benefit clearly outweighs the risk.

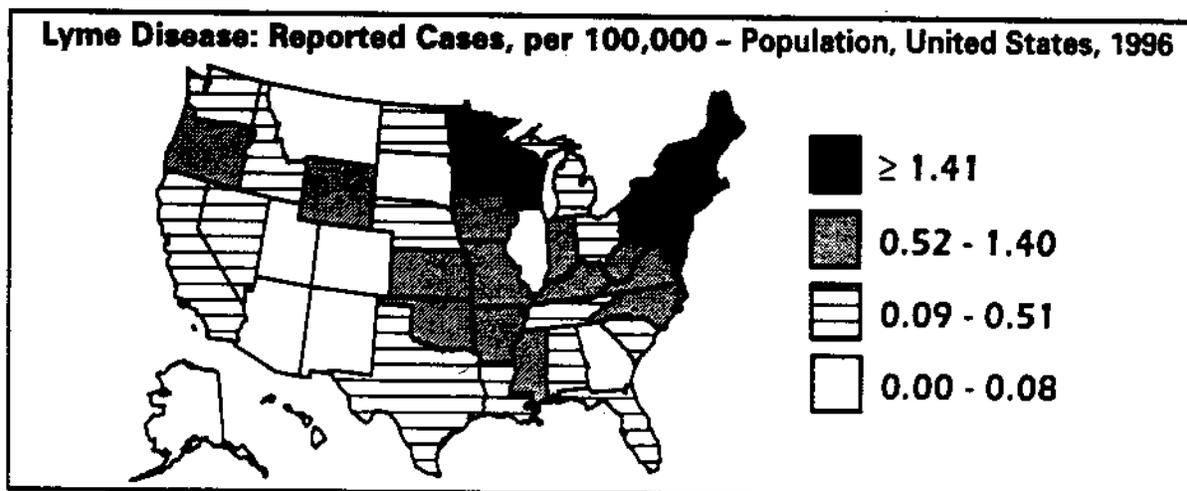
Vaccination with the Lyme disease vaccine may induce a false-positive ELISA result for *B. burgdorferi* infection. Anti-OspA antibodies can be detected by ELISA for *B. burgdorferi*. Because vaccination may result in a positive IgG ELISA in the absence of infection, Western blot testing should be performed if the ELISA is positive or equivocal in vaccinated individuals being evaluated for Lyme disease.

**DOSING:** The recommended vaccination schedule consists of 30 mcg/0.5 mL doses administered intramuscularly at 0, 1 and 12 months. It should be administered intramuscularly in the deltoid region. The CDC has recommended that administration be targeted for several weeks prior to the onset of the spring tick-feeding season.

**PRODUCT AVAILABILITY:** The Lyme disease vaccine received FDA approval in December 1998. It is available as a sterile suspension in single-dose vials and prefilled syringes for intramuscular administration. The vaccine should be stored under refrigeration (21 to 81C, 361 to 461F). The vaccine should be discarded if it has been frozen. It must be shaken prior to administration to ensure a uniform suspension. Each 0.5 mL dose contains 30 mcg of lipoprotein OspA adsorbed onto 0.5 mg aluminum as aluminum hydroxide adjuvant, plus 10 mM phosphate buffered saline and 2.5 mg of 2-phenoxyethanol, a bacteriostatic agent.

**CONCLUSION:** The Lyme disease vaccine is highly effective in preventing Lyme disease in regions where Lyme disease is endemic. Lyme disease is not a contagious disease, so vaccination does not induce herd immunity and thereby benefit a larger portion of society. Also, it is a disease that generally responds well to antibiotic therapy, particularly in the early stages. Use of the vaccine should be considered for individuals at high risk for Lyme disease due to significant exposure to tick habitats in endemic regions. Use of the vaccine should not be recommended for those who do not meet this criterion.

While an abbreviated dosing schedule may produce similar antibody titers after the last dose, it is unknown if the duration of protection will be the same as the FDA-approved schedule. The duration of protection provided by any of the dosing schedules is unknown, and the timing or need for booster doses remains to be established.



Source: CDC<sup>3</sup>

## ZALEPLON - SONATA™ (Wyeth-Ayerst Laboratories 1S)

**INDICATIONS:** A New Drug Application (NDA) has been filed for the use of zaleplon in the treatment of insomnia in adults.

The class labeling of hypnotic agents indicates that their use should be limited to 7 to 10 days. Reevaluation of the patient is recommended if the hypnotic agent is needed for more than 2 to 3 weeks. These agents should not be prescribed in quantities exceeding a 1-month supply.

**CLINICAL PHARMACOLOGY:** Zaleplon (CL 284,846) is a pyrazolopyrimidine derivative non-benzodiazepine hypnotic. Like zolpidem, it is selective for the benzodiazepine BZ<sub>1</sub> (omega <sub>1</sub>) receptor subtype and has sedative, anxiolytic, muscle relaxant and anticonvulsive effects. In animal studies, it has induced muscle relaxation, increased EEG sleep, exerted anticonvulsant effects, decreased locomotor activity and produced motor deficits. In addition, it has a lack of next-day hangover effects and amnesic effects, minimal potentiating effect with alcohol and a lack of rapid tolerance to the sedative effects.

Zaleplon is less potent than zolpidem: placebo < zaleplon 10 mg < zaleplon 20 mg < zolpidem 10 mg < zolpidem 20 mg. Zaleplon 10 and 20 mg and zolpidem 10 and 20 mg produced greater sedation than placebo in healthy young adults. Both doses of zolpidem produced greater sedation than either zaleplon dose. Subjects returned to baseline by 5 hours after zaleplon administration compared to 8 hours after zolpidem. Zaleplon and lorazepam reduced psychomotor performance; zaleplon 20 mg had an effect for at least 3 hours after the zaleplon dose and 5 hours after lorazepam 2 mg in healthy volunteers. Both agents also impacted working and secondary memory, although recovery was also faster with zaleplon than lorazepam.

**PHARMACOKINETICS:** Peak plasma concentrations are reached within 1 to 1.5 hours following oral administration.<sup>5,8</sup> Peak levels of the major metabolite CL 284,859 are reached within 1.1 hours. Bioavailability is approximately 30%, presumably due to extensive first-pass metabolism.

The half-life of zaleplon is 1 hour. The half-life of its major metabolite, CL 284,859, is 1 to 1.4 hours. The major metabolite is not an effective hypnotic agent. Less than 0.1% of the dose is excreted unchanged in the urine or as the major metabolite.

Zaleplon is metabolized by the cytochrome P450 3A isoform.

Table 1: Pharmacokinetics of Selected Sedative/Hypnotic Agents:

Parameter	Triazolam	Zaleplon	Zolpidem
Time-to-peak concentration	2 h	1-1.5 h	1.6 h
Elimination half-life	1.5-5.5 h	1 h	2.5 h
Half-life in elderly	*		2.9 h*
Half-life in hepatic dysfunction			9.9 h*
Half-life in renal dysfunction			2.5 h

\* Dosage adjustments recommended

**EFFICACY:** Zaleplon was compared with zolpidem and placebo in a double-blind study enrolling 598 outpatients with insomnia. Patients received zaleplon 5 mg, 10 mg or 20 mg, zolpidem 10 mg or placebo for 28 consecutive nights followed by three nights of placebo and four nights of no treatment. Each morning participants completed post-sleep questionnaires estimating time to sleep onset, total time slept, number of awakenings and sleep quality. Shorter sleep latencies were observed with increasing doses of zaleplon, with effects persisting throughout the 4-week study. Zaleplon 20 mg was more effective than zolpidem 10 mg in decreasing sleep latency. Only zaleplon 20 mg was more effective than placebo with regard to total time slept, number of awakenings and sleep quality. Rebound insomnia was observed in the zolpidem-treated patients on the first night after discontinuation. A similar study compared zaleplon 5 mg, 10 mg or 20 mg, zolpidem 10 mg and placebo in 574 patients with primary insomnia or mild insomnia associated with mild nonpsychotic psychiatric disorders. Following a 7-night placebo baseline phase,

subjects received zaleplon, zolpidem or placebo for 28 nights followed by three nights of placebo and four nights with no treatment. Median sleep latency during week-1 was reduced to 42 minutes with zaleplon 5 mg, 36 minutes with zaleplon 10 mg, 33 minutes with zaleplon 20 mg, compared to 50 minutes with placebo. Zolpidem also reduced sleep latency, although specific effects were not reported. Rebound insomnia was not observed following discontinuation of zaleplon, but was observed after discontinuation of zolpidem. Sleep duration was increased with zaleplon 20 mg and with zolpidem.

Zaleplon and triazolam were compared in a double-blind, placebo controlled trial enrolling 132 patients with primary insomnia. Following a 3-day placebo baseline period, patients received zaleplon 5 mg or 10 mg, triazolam 0.25 mg or placebo for 14 nights followed by two discontinuation nights on placebo. Median latency to persistent sleep was shorter in both zaleplon groups and the triazolam group compared to placebo during the first week of therapy, but not during the second week due to a significant placebo effect. The effects of zaleplon on sleep latency were similar in the first and second weeks. Total sleep time did not differ between the zaleplon and placebo groups. Sleep architecture was not altered in either the zaleplon or triazolam groups. Total sleep time was increased during the first week of triazolam treatment, but not the second. On subjective assessment of sleep latency, zaleplon 10 mg and triazolam were more effective than placebo during the first week. Only zaleplon 10 mg produced a lower subjective sleep latency during the second week, and on the last nights of assessment none of the active treatments were judged more effective than placebo. Negative residual morning psychomotor or memory effects were not observed in any treatment group.

Zaleplon was also evaluated in a double-blind, placebo controlled, dose-response study enrolling 137 patients with primary insomnia. Patients received zaleplon 2 mg, 5 mg, 10 mg or 20 mg or placebo. Patients were evaluated over 10 consecutive nights in a sleep lab: three screening nights on placebo, five treatment nights on zaleplon or placebo and two discontinuation nights on placebo. Latency to persistent sleep was consistently reduced in the zaleplon 5 mg, 10 mg and 20 mg groups compared to placebo. Total sleep time was consistently increased only in the zaleplon 20 mg group. Sleep latency was reduced by about 35 minutes, and total sleep time was increased by about 42 minutes in the zaleplon 20 mg group compared to baseline. No evidence of rebound insomnia was observed in any treatment group.

Another double-blind, placebo controlled study evaluated zaleplon 5 and 10 mg in 422 patients at least 65 years of age with primary insomnia. Following a 7-day placebo baseline period, patients received zaleplon 5 mg, zaleplon 10 mg or placebo before bedtime for 14 days, followed by another 7-day placebo phase. During the first week of treatment, the median time to sleep onset was reduced from 62 minutes to 43 minutes in the zaleplon 5 mg group and from 71 minutes to 40 minutes in the zaleplon 10 mg group. The median time to sleep onset did not change in the placebo group. The effects on sleep latency were maintained in the second week. Sleep quality was also improved with both zaleplon doses compared to placebo. No difference between the zaleplon doses was observed. No differences between zaleplon and placebo were observed for total time slept or number of awakenings. Rebound insomnia did not occur.

The effects of zaleplon on sleep quality, memory functions and actual driving performance were compared with those of zopiclone and placebo in a double-blind, crossover design study enrolling 28 volunteers. Subjects received capsules twice on each treatment night: one before bedtime and one after being briefly awoken 5 hours later. Treatments were placebo both times, zaleplon 10 or 20 mg followed by placebo, placebo followed by zaleplon, zopiclone 7.5 mg followed by placebo or placebo followed by zopiclone. Subjects arose 3 hours after the second dose. Sleep quality was reported improved with each active treatment. Zopiclone hindered awakening and adversely affected mood. The early zaleplon dose had no effects on memory or driving performance. The late zaleplon dose affected memory, but not driving performance. Both early and late zopiclone doses impaired driving.

Next day sedation after nighttime administration of zaleplon, flurazepam and placebo was compared in 93 healthy adults without insomnia. Patients received zaleplon 10 mg, zaleplon 20 mg, flurazepam 30 mg or placebo, then underwent two overnight sleep studies with next day multiple sleep latency tests and psychomotor performance tests. Sleep architecture was not altered following zaleplon administration compared to placebo; a slight reduction in REM percent was observed with flurazepam. Sleep latency times did not differ between zaleplon and placebo, but they were greatly reduced with flurazepam, indicating substantial next day sedation. While next day sleep latency times were not reduced following

placebo or zaleplon administration, the mean multiple sleep latency time was reduced from 13.6 at baseline to 5.62 after flurazepam. Psychomotor impairment was also observed with flurazepam but not zaleplon.

**ADVERSE REACTIONS:** The most common adverse effects have included dizziness, blurred vision, loss of energy, fatigue, loss of concentration, impaired cognition, impaired motor skills, drowsiness and diarrhea. Adverse effects have also included headache, hallucinations, impaired balance and nystagmus.

Data submitted to the FDA included safety data on more than 2,800 patients treated with zaleplon, including 300 patients treated for at least 6 months.

**DRUG INTERACTIONS:** Inhibitors of CYP 3A may increase the serum concentrations of zaleplon. This action prolongs the duration of zaleplon clinical effects or increases the risk of dose-related side effects.

**RECOMMENDED MONITORING:** Zaleplon, like other sedative/hypnotic medications, is likely to be approved only for short-term use. As with other hypnotic agents, patients should be evaluated for unrecognized physical or psychiatric disorders if they require the use of this product for more than 7 to 10 days. In addition, patients should be monitored for excessive sedation, memory impairment and daytime residual sedation that might be associated with the use of these products.

**DOSING:** The optimal dose has not been established at this time. Doses of 2 to 60 mg have been evaluated, with results of doses of 10 mg or 20 mg most extensively reported.

**PRODUCT AVAILABILITY:** Wyeth-Ayerst Laboratories filed an NDA for zaleplon in February 1998. The FDA must take action of some kind by the 1999 anniversary of the filing date.

**CONCLUSION:** Zaleplon will offer an alternative to zolpidem and benzodiazepines (especially triazolam) in the short-term treatment of insomnia. Further comparative studies are necessary, however, to determine its role in the sedative market.

**Sleep History**

Answers to the following questions can help characterize the nature of the sleep disorder and narrow the differential when you are discussing the problem with the patient. If you prefer, convert the list into a sleep history questionnaire to be filled out by the patient.

1. What bothers you most about your sleep habits?
2. How long have you had trouble sleeping, and what do you think started the problem?
3. How would you describe your usual night's sleep? What time do you go to bed, and what time do you get up?
4. What do you do in the few hours before bedtime?
5. Do you follow the same sleep pattern during the week and on weekends? If not, how are weekends different?
6. How well do you sleep on the first few nights when you're away from home? Do you sleep better in a room other than the bedroom?
7. What is your bedroom like?
8. What drugs do you take? Have you ever taken sleep medications? If so, which ones?
9. Do you have physical aches and pains that interfere with sleep?
10. Do you ever feel discomfort or a "fidgety" sensation in your legs and feet when you lie down? Do you have to get up and walk around to relieve the feeling?
11. Do you ever have trouble breathing when you lie down or awaken because it is hard to breathe? Does your bed partner or roommate mention that you snore loudly?
12. Do you ever awaken with a choking sensation or a sour taste in your mouth?
13. Do you awaken in the night to use the bathroom, or do you use the bathroom because you are already awake?
14. How have you been feeling emotionally? Does your life seem to be going as well as you would like?

## **"Sleep Hygiene"**

### **Tips for Better Sleep**

1. **Go to bed and rise at about the same time everyday. Establishing a schedule helps regulate the body's inner clock. Also, try to establish a sleep routine by following the same bedtime preparations each night, thereby telling yourself it is bedtime before you get into bed.**
2. **Make sure your sleep conditions, including your bed and the room temperature are as comfortable as possible. If you share your bed with a snoring, cover-stealing, or restless partner, make separate, temporary sleeping arrangements until you re-establish a satisfactory sleeping pattern.**
3. **Wear loose-fitting or no night clothes. The more comfortable you are, the better.**
4. **Put the lights out immediately as you retire. Keep the bedroom dark. If street lights shine in your room or if you must sleep during the day, use room-darkening shades or blinds. What about the lighted clock radio that glows brightly beside the bed?**
5. **Occasional loud noises (eg, aircraft or traffic sounds) disturb sleep, even in people who do not awaken and who cannot remember the noise in the morning. Keep your bedroom as quiet as possible. If you cannot block outside noises, "cover" them with a familiar inside noise such as the steady hum of a fan or other appliance. Heavy curtains or earplugs might also be helpful for people who sleep near excessive noise.**
6. **Hunger may disturb sleep. A light snack (especially warm milk) seems to help individuals fall asleep. However, avoid late, heavy meals.**
7. **Although small amounts of alcohol (1 drink) may help induce sleep, the chronic use of large quantities leads to disturbed sleep and depression. Avoid taking an alcoholic drink directly before bedtime. When alcohol wears off during the night, you may experience periods of wakefulness.**
8. **Avoid too much mental stimulation during the hour or so before bedtime. Establish a relaxing presleep ritual, read a light novel, watch a relaxing television program, take a warm bath, or try progressive relaxation. Do not finish office work or discuss family finances with your spouse.**
9. **Avoid using your bedroom for working or watching television. Learn to associate that room with sleep and intimacy.**
10. **If you cannot sleep after 20 - 30 minutes, get up and pursue some relaxing activity such as reading or knitting until you feel sleepy; do not lie in bed worrying about getting sleep. Repeat as often as required.**
11. **Avoid daytime napping which tends to fragment sleep at night.**
12. **Many beverages stimulate the body and disturb sleep. Avoid all caffeine-containing**

beverages after 12 noon. Remember that many soft drinks, as well as coffee and tea, contain caffeine.

13. Try to get some exercise each day. Regular walks, bicycle rides, or whatever exercise you enjoy may help you sleep better. However, avoid vigorous exercise immediately before bedtime.

## MODAFINIL -PROVIGIL™ (Cephalon) 1S

**INDICATIONS:** Modafinil is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.

Table 1: FDA-Approved Indications for Various CNS Stimulants:

Drug	FDA-Approved Indication		
	Narcolepsy	Attention Deficit Disorders	Obesity
Amphetamine/Dextroamphetamine ( <i>Adderall</i> )	X	X	
Dextroamphetamine ( <i>Dexedrine</i> )	X	X	
Methamphetamine ( <i>Desoxyn</i> )		X	X
Methylphenidate ( <i>Ritalin</i> )	X	X	
Modafinil ( <i>Provigil</i> )	X		
Pemoline ( <i>Cylert</i> )		X	

**CLINICAL PHARMACOLOGY:** Modafinil is a wake-promoting agent chemically and pharmacologically unrelated to methylphenidate, amphetamine or pemoline. The precise mechanism of action of modafinil is unknown. Modafinil may produce its wake-promoting effects indirectly by decreasing GABA-mediated neurotransmission. In animal studies, modafinil reduces GABA release in the cerebral cortex, intermediate nucleus accumbens, and the sleep-related brain regions such as the medial preoptic area and the posterior hypothalamus. These effects are blocked by serotonin antagonists, suggesting serotonergic mechanisms may mediate modafinil-induced inhibition of GABA release. *In vitro* it binds to the dopamine reuptake site and increases extracellular dopamine, but does not increase dopamine release. It does not enhance dopaminergic activity and is not a direct- or indirect-acting dopamine receptor agonist. Unlike amphetamine, the wakefulness induced by modafinil is not antagonized by the dopamine antagonist haloperidol. Modafinil also is not a direct or indirect alpha<sub>1</sub>-adrenergic agonist and does not exert sympathomimetic activity. An intact central alpha<sub>1</sub>-adrenergic system appears necessary for modafinil activity, however, because modafinil-induced wakefulness can be attenuated by the alpha<sub>1</sub>-adrenergic antagonist prazosin. Modafinil does not bind to norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin or benzodiazepine receptors. It also does not inhibit the activities of monoamine oxidase B or phosphodiesterases II-V. EEG testing demonstrated an increase of alpha activity, decrease of delta and theta and very fast beta activity, and a trend towards an increase of slow beta activity with modafinil therapy, which are viewed as improvements in vigilance. Improvements in vigilance have also been observed with psychometric and psychobiological tests. Modafinil also increases locomotor activity in animals, and produces psychoactive and euphoric effects, alterations in mood, perception and thinking and feelings typical of other stimulants. It is also reinforcing and therefore potentially addicting.

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, cataplexy and rapid eye movement (REM) sleep abnormalities. A strong genetic association, particularly with the HLA-DQw1 and the HLA-DR2 antigens, is evident. Patients with narcolepsy may fall asleep regularly in passive situations, but may also fall asleep in situations where sleep normally never occurs. Increasing sleepiness may lead to autonomic behavior, episodes of activity lasting up to 30 minutes associated with amnesia. Cataplexy, a sudden loss of muscle tone precipitated by strong emotion such as laughter, occurs with variable frequency and severity. Nocturnal sleep is also commonly disrupted, and sleep apnea and periodic limb movements during sleep commonly occur.

In the treatment of narcolepsy, CNS stimulants, most commonly methylphenidate, amphetamines and pemoline, are used to reduce excessive daytime sleepiness and sleep attacks. Dextroamphetamine and methylphenidate are the most effective agents. CNS stimulants may also reduce cataplexy. Selegiline provides alerting effects and potent activity against cataplexy. Other agents used for excessive daytime sleepiness include mazindol and phentermine. Tricyclic antidepressants and the selective serotonin reuptake inhibitors are also used to control cataplexy; although less commonly, viloxazine, clonidine and gamma-hydroxybutyrate are used to reduce

cataplexy. In addition to medications, a number of nonpharmacologic tools are often useful in the management of narcolepsy such as keeping a regular sleep-wake schedule, taking from 1 to 5 daily 10- to 20-minute naps, scheduling activities at times of the day with less sleepiness and the avoidance of symptom-triggering situations.

**PHARMACOKINETICS:** Modafinil is a racemic compound. At steady state, total exposure to the l-isomer is three times that of the d-isomer. The trough concentration consists of 90% l-isomer and 10% d-isomer. Peak plasma levels are reached 2 to 4 hours after oral administration. Absorption is delayed when modafinil is administered concomitantly with food, methylphenidate or dextroamphetamine, although the extent of absorption is unaffected and the delay in absorption is unlikely to be clinically important. Pharmacokinetics are linear at doses from 50 to 400 mg. Elimination half-life of modafinil is 11.3 to 15 hours. The half-life of the l-isomer is three times that of the d-isomer. Elimination half-life of modafinil acid is 6 hours and that of modafinil sulfone is 37.6 hours. Modafinil is extensively metabolized in the liver to two major inactive metabolites, modafinil acid and modafinil sulfone, and several minor metabolites which also appear inactive. Metabolism is via hydrolytic deamidation, S-oxidation, aromatic ring hydroxylation and glucuronide conjugation. The formation of modafinil sulfone is mediated by CYP 3A4. The metabolites are renally excreted. Less than 10% of the administered dose is eliminated unchanged.

Clearance of modafinil may be reduced in the elderly. In patients with severe renal failure (creatinine clearance < 20 mL/min), modafinil pharmacokinetics were not altered; however, exposure to the inactive metabolite modafinil acid was increased nine fold. In patients with hepatic cirrhosis, modafinil clearance was reduced 60%, and the steady concentration was doubled compared to normal patients. Dosage reductions are recommended in patients with severe hepatic impairment.

Modafinil is an hepatic enzyme inducer. After chronic administration of daily doses of 400 mg or greater, modafinil induces its own metabolism. Induction of CYP 3A4 has been observed *in vitro*. Modafinil inhibits CYP 2C19. Elevated levels of tricyclic antidepressants may be observed in patients deficient in CYP 2D6, as CYP 2C19 is an ancillary pathway for the metabolism of some tricyclics (eg, clomipramine and desipramine) that are primarily metabolized by CYP 2D6. Following the initiation of modafinil, elevated levels of clomipramine have been observed in one patient demonstrated to be a CYP 2D6 poor metabolizer. *In vitro* studies also suggest modafinil may inhibit CYP 2C9.

**COMPARATIVE EFFICACY:** The results of two 9-week placebo controlled studies evaluating modafinil in patients meeting the ICD-9 and American Sleep Disorders Association criteria for narcolepsy are summarized in the modafinil package insert. Each study evaluated modafinil at doses of 200 mg per day and 400 mg per day compared to placebo, but the number of patients in each study was not disclosed in the product labeling. Both studies demonstrated improvement in excessive daytime sleepiness with both modafinil doses compared to placebo. Mean sleep latency on the Maintenance of Wakefulness Test (MWT) compared to placebo was increased by 47% to 76% by modafinil ( $p < 0.001$ ). Improvement as assessed by the Clinical Global Impression of Change (CGI-C), was reported in 58% to 72% of modafinil-treated patients compared to 37% to 38% of placebo-treated patients ( $p < 0.01$ ). Nighttime sleep was not affected.

The results of a large multicenter, placebo controlled, double-blind, randomized, parallel-group clinical trial conducted in the United States were published.\* Men and women diagnosed as having narcolepsy based on the International Classification of Sleep Disorder were invited to participate in this trial if they had:

- Recurrent daytime naps or lapses into sleep occurring almost daily for at least 3 months
- Sudden bilateral loss of postural muscle tone in associated with cataplexy
- Less than 8 minutes of sleep latency on the mean sleep latency test (MSLT)
- Excessive somnolence or sudden muscle weakness plus associated sleep paralysis, hypnagogic hallucinations, automatic behaviors, or disrupted major sleep episode and an MSLT sleep latency of less than 5 minutes.

Patients were excluded from this study if they:

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\* The results of this trial were also combined with the results of other clinical trials and are presented as summary data in the product labeling.

- They were using drugs or substances that had psychotropic effects within 14 days
- Prior adverse reaction to CNS stimulants
  - Active gastrointestinal, cardiovascular, hepatic, renal, hematological, neoplastic, endocrine, neurological (other than narcolepsy/cataplexy), respiratory or psychiatric disorders
  - Unable or unwilling to temporarily discontinue antiepileptic medications.

Patients were then randomized to placebo, modafinil 200 mg or modafinil 400 mg for 9 weeks. The study medication was given as four 100 mg capsules once daily, 30 to 45 minutes after the morning meal. Subjects assigned to the 400 mg dosage regimen were initially given 200 mg the first day and 400 mg during the remainder of the study. Patients were evaluated at the end of weeks 1, 3, 6 and 9. The assessment of effectiveness was done using the ESS, MSLT, MWT and CGI. In addition, nocturnal polysomnography, EEG, electrooculogram, electromyogram, electrocardiogram, arterial hemoglobin oxygen saturation and respiratory flow and effort were assessed. After completion of the double-blind phase of the trial and a 2-week treatment discontinuation period, patients were then allowed to enter a non-blinded, open-label treatment phase. These patients were treated with modafinil 200 to 400 mg per day, adjusted in 100 mg increments by the investigator.

Two-hundred eighty-five patients were enrolled in the study. The safety and clinical laboratory data are based on 273 patients and the effectiveness data are based on 273 patients. The completion rate was 93% with placebo, 97% with modafinil 200 mg and 85% with modafinil 400 mg; five patients were not included in the placebo data because of early discontinuation, three in the modafinil 200 mg group and 14 in the modafinil 400 mg group. Adverse effects were the main reason for early discontinuation in the modafinil 400 mg group. Mean sleep latency on the MSLT after 9 weeks was 3.3 minute (+17.9%) with placebo, 4.7 minutes (+62.1%) with modafinil 200 mg ( $p < 0.001$ ) and 5.2 minutes (+57.6%) with modafinil 400 mg ( $p < 0.001$ ). The mean sleep latency for MWT was 5.1 minutes (-12.1%) with placebo, 8.1 minutes (+39.7%) with modafinil 200 mg ( $p < 0.001$ ) and 8.9 minutes (+34.8%) with modafinil 400 mg ( $p < 0.001$ ). The percent of patients whose CGI scores improved after 9 weeks was ~37% with placebo, ~65% with modafinil 200 mg and ~74% with modafinil 400 mg.

Two-hundred thirty-eight patients opted to enroll in the open-label phase of the study. Preliminary results from this study indicate that most patients treated with modafinil had an improvement in their CGI and ESS and only 14% withdrew because of a lack of effectiveness. The drug is well tolerated, while only 11% withdrawing because of adverse effects.

Modafinil was evaluated in 50 patients with narcolepsy in a double-blind, crossover study. Patients exhibited daytime sleepiness and cataplexy, a mean sleep latency of less than 7 minutes and two or more sleep onset rapid eye movement (REM) episodes on the multiple sleep latency test, and an association with HLA DR2-DQ1. All drugs with psychostimulant effects were discontinued at least 14 days. Modafinil was administered at a dose of either 100 mg in the morning and 200 mg at noon, or 200 mg in the morning and 100 mg at noon. A 2-week placebo-treatment period was followed by modafinil or placebo therapy for 4 weeks, then by another 2-week placebo period and another 4-week treatment period during which the opposite treatment was administered. Modafinil treatment was associated with a reduction in the number of episodes of sleepiness (0.95 vs 1.3,  $p = 0.05$ ) and the duration of daytime total sleep time (0.53 h vs 0.78 h,  $p = 0.0002$ ), but did not alter night total sleep time, duration of wake time after sleep onset or the number of night awakenings. Visual analog scales did not show any modification of feelings on awakening, such as sleepiness, irritability, tiredness or fitness, and the sleep questionnaire did not reveal any modification of sleep continuity or quality. Despite these findings, both physicians and patients reported an overall clinical benefit with modafinil compared to placebo. Approximately half of the patients were described as good responders. Maintenance of wakefulness testing (MWT), an evaluation of excessive daytime sleepiness, demonstrated improvements with modafinil therapy. More side effects were reported with placebo treatment.

Modafinil was also evaluated as a treatment for excessive daytime sleepiness in a study enrolling 94 patients with narcolepsy, 23 patients with hypersomnia and 6 patients with disrupted nocturnal sleep and excessive daytime sleepiness. Patients received modafinil 200 to 400 mg/day, as divided doses administered upon awakening and at noon. Among 37 patients with narcolepsy with cataplexy who continued modafinil for a mean of 32 months, efficacy was described as excellent in 10 patients (27%), good in 23 patients (63%) and fair in 4

patients (11%). Disrupted nocturnal sleep was reported by 41 patients with narcolepsy, of whom 9 (22%) reported improvement with modafinil. Three patients reported cataplexy reduction. Eleven patients with narcolepsy without cataplexy continued modafinil for a mean of 26 months. Improvement in daytime sleepiness was described as excellent in four patients and good in seven. Four of 18 patients reported disrupted nocturnal sleep, which improved in two patients with modafinil. Twelve patients with hypersomnia continued modafinil for a mean of 29 months. Improvement in excessive daytime sleepiness was excellent in four patients and good in eight. Three patients with disrupted nocturnal sleep and excessive daytime sleepiness continued modafinil for a mean of 6 months. Reduction in excessive daytime sleepiness was described as excellent in one patient and good in two. Beneficial effects of modafinil have been described in several additional uncontrolled studies enrolling patients with narcolepsy, idiopathic hypersomnia and insomnia.

One hundred and forty patients with narcolepsy-cataplexy were treated with modafinil in an open-labeled study. The dose of modafinil was 200 to 400 mg per day taken in divided doses after awakening and at noon. The improvement in daytime sleepiness was classified as good to excellent in 64.1% of the patients. Modafinil therapy appears to be effective in long-term therapy since only 37.8% of patients had interrupted their treatment after a mean of 2 years of therapy. Loss of efficacy was the main reason patients discontinued modafinil therapy; 62.3% as the main reason and 81.1% associated with other factors. The other most common reason for discontinuation was adverse effects: 11.3% as the main reason and 28.3% associated with other factors such as loss of efficacy. The overall incidence of adverse reactions was 22.8%.

In a review of narcolepsy therapies, modafinil was judged to be less effective than dextroamphetamine and methylphenidate in producing clinical improvement. Modafinil does not reduce stage 2 sleep or REM sleep, unlike the amphetamines, and night sleep is not modified on modafinil. Subjective sleep quality is impaired by amphetamines, but not modafinil. Unlike amphetamines, blood pressure and heart rate are usually not altered by modafinil.

In a pilot study enrolling six patients with obstructive sleep apnea-hypopnea syndrome, modafinil reduced daytime sleep duration, lengthened the duration of subjective daytime vigilance and improved long-term memory. Night sleep and respiratory function were not affected. Modafinil also improved clinical outcome and normalized EEG in patients with alcoholic brain syndrome.

Because of its favorable side effect profile, it may also find a role as an anti-fatigue agent in the military and for civilians in critical jobs requiring night shift work.

**CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:** The contraindications, warnings and precautions included in the labeling for the CNS stimulants are summarized in Appendix I.

Modafinil is contraindicated in patients with a history of allergic reactions to the drug, lactose, corn starch, magnesium silicate, croscarmellose sodium, povidone, magnesium stearate and talc.

The recommended precautions for modafinil therapy include:

- Functional impairment in judgment, thinking and motor skills may occur.
- Caution should be used in operating automobile or other hazardous machinery.
- Chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG may occur in patients with mitral valve prolapse or left ventricular hypertrophy.
- Therapy should be avoided in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or manifestations of mitral valve prolapse with CNS stimulant use.
- If possible, modafinil therapy should be avoided in patients with a recent history of myocardial infarction or unstable angina.
- Blood pressure should be monitored in patients with hypertension.
- Modafinil should be used with caution in patients with a history of psychosis.
- Higher plasma levels of modafinil's metabolites may occur during severe renal dysfunction; the effects of these elevated plasma levels are unknown.
- Modafinil dose should be decreased in patients with severe hepatic impairment.
- Dosage reductions may be necessary in elderly patients, due to decreased renal or hepatic function.

- Effectiveness of oral contraceptives may be decreased during and for 1 month after discontinuation of modafinil therapy.

Modafinil is categorized in Pregnancy Category C. Embryotoxicity was apparent in some animal models.

**ADVERSE REACTIONS:** The most common side effects associated with modafinil are headache, infection, nausea, nervousness, anxiety and insomnia. Side effects have included headache, depression, nervousness, anxiety, cataplexy, paresthesia, dyskinesia, hypertonia, dry mouth, amblyopia, abnormal vision, nausea, anorexia, vomiting, diarrhea, abnormal liver function, rhinitis, pharyngitis, dyspnea, inner tension, headache, dizziness and flushing. Other side effects included tachycardia, sweating, bad temper, dysphoria, chest pain, neck pain, dysmenorrhea, chills, hypotension, hypertension, vasodilation, excitation, fatigue, hyperglycemia, albuminuria, sexual hyperactivity, weight gain and euphoria. A complete list of adverse effects reported with modafinil therapy can be found in the product labeling. No consistent changes in body weight have been observed.

Some of the reports have indicated that modafinil has no acute effect on tension-anxiety, anger-hostility, confusion-bewilderment, sleep quality, blood pressure or heart rate. Other reports have included at least some of these as potential side effects associated with modafinil therapy. Even the reports that claim modafinil therapy was not associated with these side effects have included nervousness and anxiety as adverse reactions occurring more frequently with modafinil than placebo.

In a study comparing the abuse potential of modafinil and methylphenidate in subjects experienced with drugs of abuse, modafinil produced psychoactive and euphoric effects and feelings comparable to those of methylphenidate. It may be less likely to produce euphoria than dextroamphetamine or methylphenidate.

A young female ingested 4,500 mg of modafinil in a suicide attempt. Side effects were limited to tachycardia, excitation and insomnia. Another individual intentionally took a dose of 4,000 mg, and a total of 151 doses of 1,000 mg/day or more have been taken by 32 patients. No unexpected effects have been observed. Other effects associated with high doses have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea and decreased prothrombin time.

**DRUG INTERACTIONS:** The effects of modafinil are blocked by previous administration of prazosin and presumably other  $\alpha_1$  antagonists. In animal studies, the effects of modafinil have been blocked by nonselective serotonin antagonist methysergide, 5-HT<sub>2</sub> antagonist ketanserin, partially blocked by 5-HT<sub>3</sub> antagonist bemisetron and blocked by the  $\alpha_1$  antagonist prazosin and the catecholamine store-depleting reserpine.

The effectiveness of steroidal contraceptives (including depot and implantable contraceptives) may be reduced by modafinil when used concomitantly and for 1 month after discontinuation of modafinil. Alternative or concomitant methods of contraception are recommended for patients being treated with modafinil and for 1 month after discontinuing therapy.

Modafinil is an hepatic enzyme inducer. Modafinil induces its own metabolism after chronic administration of doses of 400 mg or greater daily. Induction of CYP 3A4 has been observed *in vitro*. Levels of medications eliminated via the CYP 3A4 isozyme, such as cyclosporine, steroidal contraceptives and theophylline, may be reduced with chronic concomitant modafinil therapy. In one patient, cyclosporine levels were reduced 50% with chronic administration of modafinil 200 mg/day. Modafinil levels may be altered by concomitant administration of modafinil with inducers of CYP 3A4 (carbamazepine, phenobarbital, troglitazone, and rifampin) and inhibitors of CYP 3A4 (ketoconazole, itraconazole). In *in vitro* studies, modafinil also induced CYP 1A2 and CYP 2B6.

Modafinil inhibits CYP 2C19. Elevated levels of tricyclic antidepressants and SSRIs may be observed in patients deficient in CYP 2D6, as CYP 2C19 is an ancillary pathway for the metabolism of some of these agents (eg, clomipramine and desipramine) that are primarily metabolized by CYP 2D6. CYP2D6 deficiency occurs in 7% to 10% of the Caucasian population and to a similar or lower extent in other populations. Following the initiation of modafinil, elevated levels of clomipramine have been observed in one patient demonstrated to be a CYP 2D6 poor metabolizer. Levels of medications eliminated via CYP 2C19, such as diazepam, phenytoin and

propranolol, may be increased during concomitant administration of modafinil.

*In vitro* studies also suggest modafinil may inhibit CYP 2C9. The patient should be monitored closely for the first several months when modafinil is administered with warfarin or phenytoin.

**DOSING:** The recommended dose of modafinil is 200 mg daily given as a single dose in the morning. Doses of 400 mg daily, given as a single dose, have been well tolerated but have not been demonstrated to be more effective than 200 mg daily

The dose should be reduced to 100 mg daily as a single dose in the morning in patients with severe hepatic impairment. A reduced dose should also be considered in the elderly. Safety and effectiveness of modafinil in children younger than 16 years of age have not been evaluated.

**PRODUCT AVAILABILITY:** Modafinil received FDA approval in December 1998. It is available as 100 and 200 mg tablets. It is classified as a Schedule IV controlled substance (see Table 2).

Table 2: DEA Classification of CNS Stimulants Used in the Treatment of Narcolepsy:

Drug	DEA Classification
Amphetamine/Dextroamphetamine ( <i>Adderall</i> )	C-II
Dextroamphetamine ( <i>Dexedrine</i> )	C-II
Methamphetamine ( <i>Desoxyn</i> )	C-II
Methylphenidate ( <i>Ritalin</i> )	C-II
Modafinil ( <i>Provigil</i> )	C-IV
Pemoline ( <i>Cylert</i> )	C-IV

**CONCLUSION:** Modafinil offers an alternative to traditional CNS stimulants in the treatment of narcolepsy. Studies directly comparing it to amphetamines and methylphenidate, currently the preferred therapies for narcolepsy, are not available.