

Primer on Fillers Emphasizes Variety, Artistry

BY DOUG BRUNK
San Diego Bureau

LAS VEGAS — When using dermal fillers, think of yourself as an artist with a palette of colors, using this one here and that one there.

“There is no ideal filler for all occasions; we need to have a range of fillers,” said Dr. Alastair Carruthers, who, with his wife Dr. Jean D.A. Car-

ruthers, pioneered the cosmetic use of botulinum toxin A. “You must always match the patient with the indication and the filler.”

At the annual meeting of the American Society of Cosmetic Dermatology and Aesthetic Surgery, he went on to discuss his approach to treating specific anatomical areas with various dermal fillers:

► **Glabella.** For this area “you have to in-

ject the frown line superficially, so you want a product that is relatively thin,” said Dr. Carruthers, who practices dermatology in Vancouver, B.C.

“Good old Zyderm was wonderful in this area, but you don’t want to inject anything that is likely to cause vascular occlusion.” For the glabella, he will typically use Restylane, Juvéderm Ultra, or Evolence Breeze in conjunction with Botox.

► **Infraorbital hollow.** He called this area the most difficult to treat consistently well. Even a tiny overcorrection can cause bumps.

“My advice is to always undercorrect,” he said. “Always inject supraperiosteally. Hyaluronic acid fillers are great in this area.” Diluted Evolence Breeze is another option.

► **Malar/zygomatic area.** For this area, the optimal filler depends on the patient’s aversion to risk. Radiesse is going to provide the patient with the best value for the money, “but you’re going to get bruising and swelling,” said Dr. Carruthers, who is also with the department of dermatology and skin science at the University of British Columbia in Vancouver.

“You’re also going to get bruising and swelling to a lesser degree with hyaluronic acid fillers. So for the individual who has a dinner party that night, I would use Evolence.”

► **Cheeks.** This is a challenging area to treat from a technical standpoint, but the



A patient is shown before receiving Radiesse for lipoatrophy of the cheeks, which can be challenging to treat.



Noticeable results can be seen in the patient’s cheek area after treatment with one syringe of Radiesse.

results for patients with HIV-associated lipoatrophy can be striking. Dr. Carruthers likes to use Radiesse, hyaluronic acid fillers such as Juvéderm Ultra Plus or Perlane, or Evolence.

► **Nasolabial folds.** Since any dermal filler works well in the nasolabial folds, Dr. Carruthers uses “whatever I have in the syringe. I will always be treating other areas and will use the filler I’m already using in the nasolabial folds.”

If someone comes in saying that they want their nasolabial folds corrected, “always look at their cheeks to see if they need improvement there as well,” he suggested.

“Also, don’t overdo it. We’ve all seen individuals who have seen their nasolabial folds corrected spectacularly. Babies have nasolabial folds. The na-

EPIDUO™

(adapalene and benzoyl peroxide) Gel 0.1% / 2.5%

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Not For Ophthalmic, Oral, or Intravaginal Use.

BRIEF SUMMARY

INDICATIONS AND USAGE

EPIDUO Gel is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided.

Erythema, scaling, dryness, and stinging/burning may occur with use of EPIDUO Gel.

ADVERSE REACTIONS

Observed local adverse reactions in patients treated with EPIDUO Gel were erythema, scaling, dryness, stinging, and burning. Other most commonly reported adverse events ($\geq 1\%$) in patients treated with EPIDUO Gel were dry skin, contact dermatitis, application site burning, application site irritation, skin irritation.

DRUG INTERACTIONS

Exercise caution in using preparations containing sulfur, resorcinol, or salicylic acid, medicated or abrasive soaps and cleansers and products with high concentrations of alcohol or astringents in combination with EPIDUO Gel. Concomitant use of topical products with a strong drying effect can increase irritation. Use with caution.

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with EPIDUO Gel. Animal reproduction studies have not been conducted with the combination gel or benzoyl peroxide. Furthermore, such studies are not always predictive of human response; therefore, EPIDUO Gel should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m²/day) the maximum recommended human dose (MRHD) of 2 grams of EPIDUO Gel. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥ 25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m²) the MRHD] exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

Nursing Mothers

It is not known whether adapalene or benzoyl peroxide is excreted in human milk following use of EPIDUO Gel. Because many drugs are excreted in human milk, caution should be exercised when EPIDUO Gel is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of EPIDUO Gel in pediatric patients under the age of 12 have not been established.

Geriatric Use

Clinical studies of EPIDUO Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, phototoxicity, genotoxicity, or fertility studies were conducted with EPIDUO Gel.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats

Rx only

at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of EPIDUO Gel. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed.

No significant increase in tumor formation was observed in rodents topically treated with 15-25% benzoyl peroxide carbopol gel (6-10 times the concentration of benzoyl peroxide in EPIDUO Gel) for two years. Rats received maximum daily applications of 138 (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area, these levels are 27-40 times the MRHD. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for rest of the 2 years study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown.

In a photocarcinogenicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV-induced tumor formation was observed in hairless mice topically treated for 40 weeks.

No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects *in vitro* (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or *in vivo* (mouse micronucleus test).

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results, mutagenic potential was observed in a few but not in a majority of investigations. Benzoyl peroxide has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, it has caused DNA-protein cross-links in the human cells, and has also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells. In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F₀ males and females, or growth, development and reproductive function of F₁ offspring. No fertility studies were conducted with benzoyl peroxide.

PATIENT COUNSELING INFORMATION

– Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply EPIDUO Gel as a thin layer, avoiding the eyes, lips and mucous membranes.

– Advise patients not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.

– EPIDUO Gel may cause irritation such as erythema, scaling, dryness, stinging or burning.

– Advise patients to minimize exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel, (e.g., hat) when exposure cannot be avoided.

– EPIDUO Gel may bleach hair and colored fabric.

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References: 1. Data on file. Galderma Laboratories, L.P. Phase 3 data. 2. Thiboutot DM, Weiss J, Bucko A, et al; Adapalene-BPO Study Group. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. *J Am Acad Dermatol.* 2007;57(5):791-799.

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peroxide) Gel 0.1% / 2.5%

solabial fold is a natural thing; you can soften it but don't try to get rid of it."

► **Lips.** This is another challenging area to treat, one "where you make or lose your reputation in your area of practice," Dr. Carruthers said.

He recommends avoiding the use of permanent fillers in the lips and those that cause fibroplasia, including Allo-Derm, and products that contain Gore-Tex.

"Why? Because the lip is so mobile. Even with the soft fillers we put into lips you can still get problems," Dr. Carruthers explained during his presenta-

tion. "Be conservative and cautious, and don't try to overtreat the lips."



'There is no ideal filler. ... You must always match the indication and the filler.'

DR. CARRUTHERS

He said that he uses Evolence Breeze about 70% of the time for correction of

the lips. He also uses Restylane and Juvéderm Ultra.

► **Marionette lines.** The area requires a relatively stiff filler such as Juvéderm Ultra Plus, Perlane, or Evolence. Even with these products, however, the results may not be optimal.

"You have to accept that fillers do not hold well in the marionette area," he said. "You should be injecting right down to the jaw line if you're attempting to improve this area."

► **Chin.** When adding volume to this area, be mindful of the branches of the facial artery. "Stay superficial where the

facial artery crosses the mandible," he recommended.

Dr. Carruthers noted that bruising is most likely to occur when the dermatologist injects into the lateral part of the chin. To minimize bruising, he recommends injecting posterolaterally from the central chin.

Fillers he uses for the chin include Radiesse, Juvéderm Ultra Plus, Perlane, or Evolence.

Dr. Carruthers disclosed that he is a consultant and performs research for Allergan Inc., Merz GmbH & Co., and Bi-form Medical Inc. ■

Enbrel® (etanercept) Brief Summary

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ENBREL® is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. ENBREL® can be initiated in combination with methotrexate (MTX) or used alone.

ENBREL® is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older.

ENBREL® is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis. ENBREL® can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

ENBREL® is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

ENBREL® is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

WARNING

RISK OF INFECTIONS

Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with ENBREL® (see **WARNINGS** and **ADVERSE REACTIONS**). Infections have included bacterial sepsis and tuberculosis. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms of infection during and after treatment with ENBREL®. Patients who develop an infection should be evaluated for appropriate antimicrobial treatment and, in patients who develop a serious infection, ENBREL® should be discontinued.

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including ENBREL®. Tuberculosis may be due to reactivation of latent tuberculosis infection or to new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL® than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL®. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating ENBREL® and during treatment. Treatment of latent tuberculosis infection should be initiated prior to therapy with ENBREL®. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving TNF blockers. Some patients who tested negative for latent tuberculosis prior to receiving ENBREL® have developed active tuberculosis. Physicians should monitor patients receiving ENBREL® for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

CONTRAINDICATIONS

ENBREL® should not be administered to patients with sepsis or with known hypersensitivity to ENBREL® or any of its components.

WARNINGS

Infections

In post-marketing reports, serious infections and sepsis, including fatalities, have been reported with the use of ENBREL®. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with ENBREL® should be monitored closely. Administration of ENBREL® should be discontinued if a patient develops a serious infection or sepsis. Treatment with ENBREL® should not be initiated in patients with active infections, including chronic or localized infections. Physicians should exercise caution when considering the use of ENBREL® in patients with a history of recurring infections or with underlying conditions which may predispose patients to infections, such as advanced or poorly controlled diabetes (see **PRECAUTIONS** and **ADVERSE REACTIONS: Infections**).

Cases of tuberculosis have been observed in patients receiving TNF-blocking agents, including ENBREL®. Tuberculosis may be caused by reactivation of latent tuberculosis infection or new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL® than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL®. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated prior to therapy with ENBREL®. Patients receiving ENBREL® should be monitored closely for signs and symptoms of active tuberculosis. The possibility of tuberculosis should be considered, especially in patients who have traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with ENBREL® should have a thorough history taken prior to initiating therapy.

In a 24-week study of concurrent ENBREL® and anakinra therapy, the rate of serious infections in the combination arm (7%) was higher than with ENBREL® alone (0%). The combination of ENBREL® and anakinra did not result in higher ACR response rates compared to ENBREL® alone (see **CLINICAL STUDIES: Clinical Response and ADVERSE REACTIONS: Infections**). Concurrent therapy with ENBREL® and anakinra is not recommended.

Neurologic Events

Treatment with ENBREL® and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed in association with ENBREL® therapy. The causal relationship to ENBREL® therapy remains unclear. While no clinical trials have been performed evaluating ENBREL® therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity.^{7,8} Prescribers should exercise caution in considering the use of ENBREL® in patients with preexisting or recent-onset central nervous system demyelinating disorders (see **ADVERSE REACTIONS**).

Hematologic Events

Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with ENBREL®. The causal relationship to ENBREL® therapy remains unclear. Although no high risk group has been identified, caution should be exercised in patients being treated with ENBREL® who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL®. Discontinuation of ENBREL® therapy should be considered in patients with confirmed significant hematologic abnormalities.

Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC < 1 x 10⁹/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

Malignancies

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving the TNF blocker compared to control patients. During the controlled portions of ENBREL® trials, 3 lymphomas were observed among 4509 ENBREL®-treated patients versus 0 among 2040 control patients (duration of controlled treatment ranged from 3 to 24 months). In the controlled and open-label portions of clinical trials of ENBREL®, 9 lymphomas were observed in 5723 patients over approximately 11201 patient years of therapy. This is 3-fold higher than that expected in the general population. While patients with rheumatoid arthritis or psoriasis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the potential role of TNF-blocking therapy in the development of malignancies is not known (see **ADVERSE REACTIONS: Malignancies**).^{11,12}

In a randomized, placebo-controlled study of 180 patients with Wegener's granulomatosis where ENBREL® was added to standard treatment (including cyclophosphamide, methotrexate, and corticosteroids), patients receiving ENBREL® experienced more non-cutaneous solid malignancies than patients receiving placebo (see **ADVERSE REACTIONS: Malignancies**). The addition of ENBREL® to standard treatment was not associated with improved clinical outcomes when compared with standard therapy alone. The use of ENBREL® in patients with Wegener's granulomatosis receiving immunosuppressive agents is not recommended. The use of ENBREL® in patients receiving concurrent cyclophosphamide therapy is not recommended.

Hepatitis B Virus Reactivation

Use of TNF blockers, including ENBREL®, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with ENBREL® should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, consideration should be given to stopping ENBREL® and initiating anti-viral therapy with appropriate supportive treatment. The safety of resuming ENBREL® therapy after HBV reactivation is controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

PRECAUTIONS

General

Allergic reactions associated with administration of ENBREL® during clinical trials have been reported in < 2% of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of ENBREL® should be discontinued immediately and appropriate therapy initiated.

Caution: The needle cap on the prefilled syringe and on the SureClick™ autoinjector contains dry natural rubber (a derivative of latex) which may cause allergic reactions in individuals sensitive to latex.

Information for Patients

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

Latex Sensitivity Allergies

ENBREL® is provided as a single-use prefilled syringe, a single-use prefilled SureClick™ autoinjector, or a multiple-use vial. The patient or caregiver should be informed that the needle cap on the prefilled syringe and on the SureClick™ autoinjector contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

Administration of ENBREL®

If a patient or caregiver is to administer ENBREL®, the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose (see the ENBREL® (etanercept) "Medication Guide"). The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes. A puncture-resistant container for disposal of needles, syringes, and autoinjectors should be used. If the product is intended for multiple use, additional syringes, needles, and alcohol swabs will be required.

Patients with Heart Failure

Two large clinical trials evaluating the use of ENBREL® in the treatment of heart failure were terminated early due to lack of efficacy. Results of one study suggested higher mortality in patients treated with ENBREL® compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with ENBREL® (see **ADVERSE REACTIONS: Patients with Heart Failure**). There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking ENBREL®. There have also been rare reports of new onset CHF, including CHF in patients

without known preexisting cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using ENBREL® in patients who also have heart failure, and monitor patients carefully.

Immunosuppression

Anti-TNF therapies, including ENBREL®, affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL®, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL® on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood (see **WARNINGS: Malignancies, ADVERSE REACTIONS: Infections, and Malignancies**). The safety and efficacy of ENBREL® in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

Most psoriatic arthritis patients receiving ENBREL® were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving ENBREL®. The clinical significance of this is unknown. Patients receiving ENBREL® may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ENBREL® (see **PRECAUTIONS: Immunosuppression**).

It is recommended that JIA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ENBREL® therapy. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL® therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoimmunity

Treatment with ENBREL® may result in the formation of autoantibodies (see **ADVERSE REACTIONS: Autoantibodies**) and, rarely, in the development of a lupus-like syndrome or autoimmune hepatitis (see **ADVERSE REACTIONS: Adverse Reaction Information from Spontaneous Reports**), which may resolve following withdrawal of ENBREL®. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with ENBREL®, treatment should be discontinued and the patient should be carefully evaluated.

Drug Interactions

Specific drug interaction studies have not been conducted with ENBREL®. However, it was observed that the pharmacokinetics of ENBREL® was unaltered by concomitant methotrexate in rheumatoid arthritis patients.

In a study in which patients with active RA were treated for up to 24 weeks with concurrent ENBREL® and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with ENBREL® alone (0%) (see also **WARNINGS**). Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC < 1 x 10⁹/L).

In a study of patients with Wegener's granulomatosis, the addition of ENBREL® to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies. The use of ENBREL® in patients receiving concurrent cyclophosphamide therapy is not recommended (see **WARNINGS: Malignancies and ADVERSE REACTIONS: Malignancies**).

Patients in a clinical study who were on established therapy with sulfasalazine, to which ENBREL® was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either ENBREL® or sulfasalazine alone. The clinical significance of this observation is unknown.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL® or its effect on fertility. Mutagenesis studies were conducted in vitro and in vivo, and no evidence of mutagenic activity was observed.

Pregnancy (Category B)

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to ENBREL®. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

Nursing Mothers

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

Geriatric Use

A total of 480 RA patients and 89 plaque psoriasis patients ages 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Pediatric Use

ENBREL® is indicated for treatment of polyarticular-course juvenile idiopathic arthritis in patients ages 2 and older. For issues relevant to pediatric patients, in addition to other sections of the label, see also **WARNINGS; PRECAUTIONS: Immunizations; and ADVERSE REACTIONS: Adverse Reactions in Patients with JIA**. ENBREL® has not been studied in children < 2 years of age.

The safety and efficacy of ENBREL® in pediatric patients with plaque psoriasis have not been studied.

ADVERSE REACTIONS

Adverse Reactions in Adult Patients with RA, Psoriatic Arthritis, Ankylosing Spondylitis, or Plaque Psoriasis

ENBREL® has been studied in 1442 patients with RA, followed for up to 80 months, in 169 patients with psoriatic arthritis for up to 24 months, in 222 patients with ankylosing spondylitis for up to 10 months, and 1261 patients with plaque psoriasis for up to 15 months. In controlled trials, the proportion of ENBREL®-treated patients who discontinued treatment due to adverse events was approximately 4% in the indications studied. The vast majority of these patients were treated with 25 mg