APhA

American Pharmaceutical Association

2215 Constitution Avenue, NW
Washington, DC 20037-2985
(202) 628-4410 Fax (202) 783-2351
http://www.aphanet.org

The National Professional Society of Pharmacists

May 17, 2001

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. 01N-0078

Dear Sir/Madam:

Thank you for the opportunity to comment on the assessment of physician and patient attitudes toward direct-to-consumer (DTC) promotion of prescription drugs. The American Pharmaceutical Association (APhA), the national professional society of pharmacists, represents more than 50,000 practicing pharmacists, pharmaceutical scientists, pharmacy students, and pharmacy technicians.

The proposed survey of attitudes toward DTC advertisements, as described in the March 19, 2001 *Federal Register*, is an important step in the continuing process to ensure that the advertising of prescription drugs is truthful and not misleading. DTC advertisements that highlight medical problems and available treatment options can be a useful source of information for patients.

In 1999, APhA adopted policy supporting legislative and regulatory activities that allow DTC advertising concerning health conditions treatable by prescription or non-prescription drug products (Attachment A). The profession recognizes the benefits of making accurate information on various health conditions and the benefits and risks of available treatment medications available to consumers. However, DTC advertisements may also confuse patients and encourage the indiscriminate use of medications. Regulations governing the content and format of DTC advertisements must be strictly enforced to safeguard patients from the potential dangers of deceptive advertisements.

APhA appreciates the Food and Drug Administration's (FDA) efforts to examine the effects of DTC advertising on both the public and health care practitioners. APhA understands that the proposed survey will include 775 patients that have visited a doctor or other health care professional in the last three months and 500 physicians that spend at least half of their time engaged in patient care. The patient survey will provide valuable information on the public's response to DTC advertising and prescription drugs in general, and the physician survey will provide insight into DTC-related patient interactions and their overall impression of DTC advertising. However, the survey overlooks other key health care practitioners who interact with patients. Pharmacists, pharmacy technicians, nurses and physician assistants also interact with patients and field

DTC-driven questions—and their insights are just as important as those of the physician. APhA strongly recommends that the Agency expand the survey beyond physicians to include pharmacists and other members of the health care team.

Pharmacy is the third largest public health profession in the United States. With 334,851 licensed pharmacists and 73,781 pharmacies in the U.S., pharmacists are the most easily accessible health care providers.[1] Pharmacists are also the leading health care authority on prescription and non-prescription medications, and are frequently the health care provider patients approach with their medication-related questions. In fact, FDA guidance on DTC advertisements recommends that pharmacists be identified in DTC advertisements as a source of drug information:

> Disclosure in the advertisement that pharmacists, physicians (or other healthcare providers), or veterinarians (in the case of animal drugs) may provide additional product information to consumers. This statement should communicate clearly that the referenced professional is a source of additional product information.[2]

In recognition of the pharmacist's role in discussing medication therapy—and thus DTC advertisements—with patients, APhA conducted a survey of pharmacists' views and opinions on DTC advertising in 1999. The survey, conducted on APhA's behalf by an independent research firm, consisted of a sample of 750 pharmacists in independent and chain pharmacy settings.[3]

According to the survey, nearly seven in ten pharmacists (67%) believe, in general, that DTC advertising provides valuable information to patients. From their responses, it is clear that DTC advertisements initiate patient inquiries concerning health issues and possible medication treatments. On average, respondents fielded 3.5 questions in a typical week from patients concerning drug products they have seen advertised. However, two-thirds of respondents also stated that they have been caught off-guard by patients asking questions about a product they were unaware the manufacturer was marketing directly to the patient. Respondents overwhelming (96%) expressed a desire that manufacturers alert pharmacists to DTC advertising campaigns *before* they are released to the public. In fact, nine in ten respondents stated that knowledge of a DTC campaign prior to its release would increase their comfort level in answering patient questions.

In response to pharmacists' concerns, APhA began providing pharmacists and other health care professionals with the information necessary to respond to questions from patients generated by DTC advertising. One method APhA has used to alert health care practitioners to DTC campaigns is called the *Direct-to-Consumer Preview*. The *DTC*

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[1] National Association of Boards of Pharmacy, *2000-2001 Survey of Pharmacy Law,* Illinois, 2000.

[2] Food and Drug Administration, *Guidance for Industry: Consumer-Directed Broadcast Advertisements*, August 1999.

[3] Survey was closed for tabulation with 500 usable responses—a 67% response rate.

Preview consists of a packet mailed to pharmacists that contains product background information, a clinical review of the product, an overview of consumer print and broadcast advertising, and frequently asked questions (See Attachment B).

APhA encourages the Agency to recognize the impact of DTC advertising on pharmacists and other health care professionals. Pharmacists are a vital part of the patient's health care team and the most knowledgeable professional about prescription and nonprescription medications. While DTC advertising may be a good mechanism to provide patients with information on health conditions and available medication treatments, it can also affect the pharmacist-patient relationship and their interactions. It is important to look at these effects as part of any study intended to examine the effects of DTC advertisements.

It is also important to examine the effects of DTC advertisements on patient attitudes towards medication use. DTC advertisements may be beneficial if they increase consumer awareness on the value of medications and stimulate patient interactions with members of the health care system. However, DTC advertisements can be harmful if they engender the impression that advertised medications are inherently safe and appropriate for casual use. APhA recommends that the Agency incorporate questions in the patient survey to assess if the benefits from DTC advertising outweigh the risks.

In conclusion, APhA supports the Agency's efforts to examine physician and patient attitudes towards DTC advertising. Periodically reviewing the effects of manufacturers' promotional activities will assist the Agency in regulating drug product promotional materials and will help ensure that patients do not receive inaccurate or misleading information. Again, APhA urges the Agency to expand the survey to include pharmacists and other members of the health care team.

Thank you for your consideration of the views of the nation's pharmacists. Please contact Susan K. Bishop, APhA's Manager of Regulatory Affairs and Political Action at 202-429-7538, or Susan C. Winckler, APhA's Group Director of Policy and Advocacy at 202-429-7533 with any questions.

Sincerely,

John A. Gans, PharmD
Executive Vice President

cc: Lucinda L. Maine, PhD, Senior Vice President, Policy, Planning, & Communications
Susan C. Winckler, RPh, JD, Group Director, Policy & Advocacy
Susan K. Bishop, Manager, Regulatory Affairs & Political Action

APhA

The National Professional Society of Pharmacists

Official Policy of the American Pharmaceutical Association

Subject: Direct-to-Consumer Advertising

Adopted: 1999

1. APhA supports legislative and regulatory activities permitting direct-to-consumer advertising concerning medical or health conditions treatable by prescription or non-prescription drug products. These advertisements must conform to rules and regulations that assure complete, comprehensive and understandable information which informs consumers of potential benefits and risks of the product.

2. APhA opposes false or misleading advertising for prescription or non-prescription drugs or any promotional efforts which encourage indiscriminate use of medication.

3. APhA supports the availability of accurate information to consumers about medication use, and recognizes the responsibility of pharmacists to provide appropriate responses to consumer inquiries stimulated by direct-to-consumer advertising as a compensated pharmaceutical care service. In addition, APhA recommends that healthcare professionals, including but not limited to pharmacists, receive new product information on DTC advertising campaigns prior to this information being made available to consumers.

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Washington, DC 20037-2985

Direct-to-Consumer **DTC PREVIEW**

APhA
The American Pharmaceutical Association
2215 Constitution Ave, NW
Washington, DC 20037
1-800-237-APhA

July 11, 2000

Dear Pharmacy Colleague:

The American Pharmaceutical Association (APhA) is pleased to provide you with its newest *DTC Preview*, describing a direct-to-consumer (DTC) campaign for Remicade® (infliximab).

Centocor, Inc., will be launching a DTC advertising program to heighten awareness of Remicade's new indication for use in combination with methotrexate to reduce the signs and symptoms of rheumatoid arthritis. APhA believes that it is essential for pharmacists to be aware of DTC campaigns to ensure that they are fully prepared to respond to consumer inquiries. This *DTC Preview* provides an overview of the Remicade campaign and background information on Remicade, including patient-directed questions and answers suitable for photocopying and distribution.

Human tumor necrosis factor alpha (TNF-α) is a key regulator of inflammation in rheumatoid arthritis. Remicade is a monoclonal antibody that binds specifically to TNF-α. It was approved initially in 1998 for the treatment of Crohn's disease; the rheumatoid arthritis indication was added late in 1999. The following key messages will be communicated to consumers through the Remicade DTC campaign:

- Remicade is a new biologic treatment for rheumatoid arthritis.
- Remicade can reduce the signs and symptoms of rheumatoid arthritis.
- Remicade offers the dosing convenience of an infusion once every eight weeks.
- Remicade infusions are covered by Medicare and most insurance carriers.

Remicade DTC advertising will appear in numerous consumer publications as well as in television commercials. Centocor already has launched the Remicade Web site at www.remicade.com; information specific to the rheumatoid arthritis indication is found at www.remicade-ra.com.

We hope that you find this information useful and look forward to providing you with future *DTC Previews.*

Sincerely,

James C. Appleby

James C. Appleby, RPh, MRH
Vice President
Professional Education and Industry Relations

Direct-to-Consumer DTC PREVIEW

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Infliximab (Remicade) approved for the treatment of rheumatoid arthritis

Infliximab (Remicade®), a monoclonal antibody against tumor necrosis factor alpha (TNF-α), now carries an indication for use with methotrexate for the treatment of patients with rheumatoid arthritis (RA) who have had an inadequate response to methotrexate alone. Infliximab was approved initially in 1998 for the treatment of Crohn's disease.

Tumor necrosis factor plays a prominent role in the pathogenesis of RA. By rendering TNF-α biologically inactive, infliximab reduces the inflammatory activity characteristic of RA and therefore reduces signs and symptoms of the disease.

The approval of this new indication for infliximab adds a second biologic response modifier to the therapeutic options for RA. Infliximab joins etanercept (Enbrel), the first biologic response modifier that was approved for RA (in fall 1998).

At a glance...

Manufacturer: Centocor
Drug class: Monoclonal antibody for rheumatoid arthritis
Indication: Used with methotrexate for the reduction in signs and symptoms of rheumatoid arthritis in patients who have had an inadequate response to methotrexate alone
Dosage: 3 mg/kg by intravenous infusion followed by 3 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter; used in combination with methotrexate
Of note:
- Infliximab should be discontinued if symptoms of hypersensitivity, such as urticaria, dyspnea, or hypotension, are observed
- Treatment may result in the formation of autoimmune antibodies; treatment should be discontinued if symptoms suggestive of a lupus-like syndrome and a positive test for antibodies are observed

Clinical trial results

The use of infliximab for the treatment of RA is supported by data from the multicenter ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy) clinical trial. This randomized, double-blind, placebo-controlled clinical trial involved 428 patients with active RA who had received continuous methotrexate for at least 3 months and at a stable dose for at least 4 weeks. Patients were assigned to receive methotrexate plus placebo or one of four regimens of infliximab. Intravenous infusions of infliximab (3 mg/kg or 10 mg/kg) were given at weeks 0, 2, and 6 followed by additional infusions every 4 or 8 weeks thereafter. The primary end point of the trial was a 20% improvement in the American College of Rheumatology (ACR) response criteria (which include select measurements of joint pain and swelling, as well as patient and physician global assessments and a laboratory marker of inflammation and pain) by week 30.

At week 30, 50% of all patients treated with infliximab and methotrexate achieved a 20% improvement from baseline, compared with only 20% of patients treated with methotrexate and placebo. In addition, 27% of all patients treated with infliximab and methotrexate achieved a 50% improvement from baseline at week 30, compared with 5% of patients who received methotrexate and placebo. Approximately 8% of patients treated with infliximab and methotrexate achieved a 70% improvement from baseline, but no patients in the methotrexate and placebo group did.

Based on 1-year radiographic data from the ATTRACT trial, Centocor (manufacturer of Remicade) is seeking an additional indication for the prevention of joint damage in patients with RA. The ATTRACT trial was unblinded at the end of the first year because of positive radiographic results.

Watch for serious infections and hypersensitivity reactions

Serious infections, including sepsis, have been reported in patients receiving TNF-blocking agents. With infliximab, many of the infections observed have been in patients receiving concurrent immunosuppressive therapy. Therefore, caution should be taken when administering infliximab to patients with a history of chronic or recurrent infection, and the drug should not be given to patients with a current infection.

Infliximab also has been associated with hypersensitivity reactions, including urticaria, dyspnea, and hypotension. Infliximab should be discontinued if severe reactions are observed. Anti-TNF therapy may result in the formation of autoimmune antibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA,

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infliximab therapy should be discontinued.

Other adverse events observed with therapy include upper respiratory infections, nausea, headache, fatigue, fever, and backache.

Infusions generally covered by insurers

The recommended dosage of infliximab for patients with RA is 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg doses at 2 and 6 weeks after the first infusion and then every 8 weeks thereafter. When used in the treatment of Crohn's disease, infliximab is administered as a single 5 mg/kg intravenous infusion to patients with moderately to severely active disease (additional doses are administered 2 and 6 weeks after the initial infusion for patients with fistulizing disease).

Because infliximab is administered as an IV infusion in a doctor's office, infusion center, or hospital, it generally is covered by insurance plans, including Medicare.

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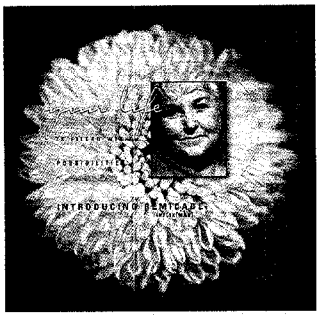
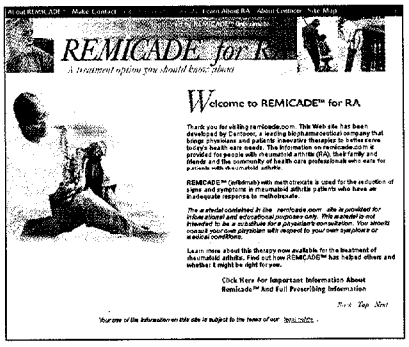
Remicade® Starter Kit
Consumers can view a video on how Remicade is administered, read literature on Remicade and rheumatoid arthritis, record their progress in a health diary, and learn about insurance coverage in the educational Starter Kit.

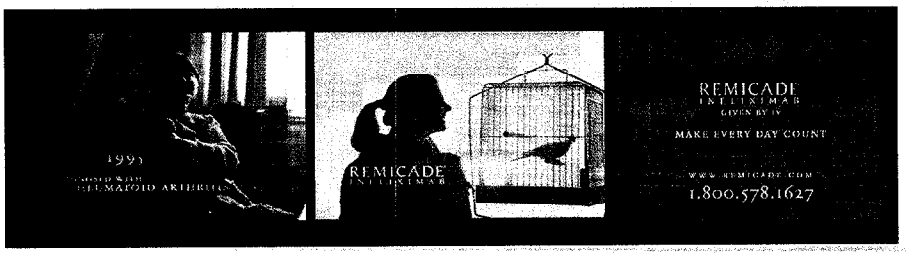
REMICADE®
INFLIXIMAB



Direct Mail
Brochures introducing Remicade were mailed directly to over 150,000 rheumatoid arthritis patients and included an 800 number for inquiries.



Web Site – www.remicade-ra.com
The Remicade Web site provides consumers with comprehensive product information, including how Remicade works, its effectiveness in controlling rheumatoid arthritis, how it is administered, and an 800 number for consumer inquiries.



Television Commercials
Remicade commercials will be televised nationally on all major networks, cable television, and satellite.

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What is rheumatoid arthritis?

Rheumatoid arthritis is an autoimmune disease—your immune system attacks the lining in your joints, resulting in inflammation, tenderness, swelling, and pain. Over time, the disease damages the cartilage and bone in your joints. The cause of rheumatoid arthritis is unknown.

What is Remicade and how does it help?

Remicade is a monoclonal antibody—a copy of an antibody that is produced naturally within the body. That antibody works against a protein in the body called tumor necrosis factor alpha (TNF-α). TNF-α is thought to play a key role in the inflammation that occurs in the joints of people with rheumatoid arthritis. By neutralizing TNF-α, Remicade reduces inflammation and can relieve swelling, tenderness, morning stiffness, and pain in your joints.

Remicade is used in people with rheumatoid arthritis who do not get adequate relief of signs and symptoms from treatment with methotrexate alone. It is not a cure for rheumatoid arthritis.

How and when do I take Remicade?

Remicade is given by intravenous (IV) infusion (into a vein). Depending on what you arrange with your health care provider, you may get the infusion in a hospital outpatient clinic, a free-standing infusion center, a doctor's office, or at home. The actual infusion takes 2 hours.

After your first infusion, you will receive another infusion 2 weeks later, and then one more 6 weeks after the first infusion. After those first three doses, you will receive an infusion every 8 weeks (6 times per year).

Will I have any side effects during the infusion?

Some patients may experience reactions during or just after the Remicade infusion. The reactions usually consist of fever, chills, or redness or itching near the injection site, and they usually are treated with medications like acetaminophen (Tylenol is one brand) or antihistamines (for example, Benadryl or Chlor-Trimeton).

Will I be able to drive myself home after my infusion?

Probably. The Remicade infusion does not cause drowsiness, so you will be able to continue with your normal schedule.

However, if you were treated with an antihistamine like Benadryl before or after the Remicade infusion, the antihistamine might make you drowsy. If you are treated with an antihistamine, ask the nurse or doctor if it is okay for you to drive. Some infusion centers may give antihistamines like Benadryl to nearly all patients to help prevent reactions, so it's always best to check.

What other side effects might I expect from Remicade?

In medical studies, Remicade was generally tolerated well by the people receiving it. The most common side effects included upper respiratory tract infections, headache, nausea, coughing, and diarrhea. Contact your doctor if these reactions are severe or persist, or if you have any unusual effects.

You may be more likely to develop infections while being treated with Remicade, especially if you are elderly. If you have a chronic infection, or a history of infections that reoccur, be sure to let your doctor know. Also, tell your doctor immediately if you develop an infection while taking Remicade.

Is it safe to take Remicade with other medications?

No drug interactions are known to occur with Remicade, but no formal studies have been conducted. In most cases, you can continue taking other drugs commonly used to treat rheumatoid arthritis while you are using Remicade. But, to be sure, tell every health care provider and pharmacist that you go to about all of the other prescription and nonprescription medications that you take. Write the names of your medications on a piece of paper—or, if you prefer, bring the containers with you when you visit your health care provider and pharmacist.

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Frequently Asked Patient Questions

Is it okay to get my annual flu shot while I am being treated with Remicade?

Talk with your doctor before getting any sort of vaccination. People being treated with Remicade should not receive "live" vaccines, because no information is available about how people react to those vaccines. The vaccines used for flu shots usually are "killed," but again, it's always best to check.

Is it safe to take Remicade if I am pregnant or breast-feeding?

Like many other drugs, Remicade should be given to a pregnant woman only if the possible benefits clearly outweigh the risks. Tell your doctor if you are or plan to become pregnant.

Because it is not known whether Remicade can pass into breast milk, your doctor may advise stopping the drug before you begin breast-feeding.

Is Remicade covered by insurance plans?

Because Remicade is administered as an IV infusion in a doctor's office, infusion center, or hospital, it is generally covered by insurance plans, including Medicare. If you have any questions about insurance coverage, it is best to call your insurance carrier or Medicare first. If you have problems getting coverage or encounter any other problems related to medical coverage for Remicade, you can call the Remicade Patient Assistance Program at 1-800-964-8345 from 9:00 am to 8:00 pm (EST) Mondays through Fridays for free assistance.

Where can I get additional information about Remicade?

Ask your pharmacist or health care provider, call the Remicade Medical Information line at 1-800-457-6399 from 8:30 am to 5:00 pm (EST) Mondays through Fridays, or go to www.remicade-ra.com on the Web.