AMERICAN COLLEGE RHEUMATOLOGY
POSITION STATEMENT

SUBJECT: FDA Labels

PRESENTED BY: Committee on Rheumatologic Care

FOR DISTRIBUTION TO: Members of the American College of Rheumatology
Medical Societies
Members of Congress
Health Care Organizations/Third Party Carriers
Insurance Companies and Commissioners
Pharmacy Benefit Managers
Managed Care Entities

POSITIONS:

1. Official Food and Drug Administration (FDA) drug labels establish parameters governing the advertising and promotion of drugs; they do not address every acceptable use of every drug and should not be regarded as the sole authority determining the standard of acceptable or accepted medical practice.

2. The guidelines in official FDA drug labels are not a substitute for sound clinical judgment and should not limit the use of therapeutics in medical practice. Rather, information in FDA labels must be interpreted by clinicians in the context of an individual patient’s condition as well as established and emerging data that are often not contained in labels.

3. Providers may lawfully recommend and prescribe FDA-labeled products for off-label indications and adjust dosing regimens beyond those outlined in the label when such use is based upon sound clinical judgment, is supported by medical evidence and is in the patient’s best interests.

4. The off-label use of pharmaceutical agents, informed by sound clinical judgment, is often medically necessary and in the patient’s best interests. This could be due to the fact that FDA-approved alternatives are lacking, or FDA-approved drugs have failed or are ill-advised due to intolerance, poor efficacy or undue risk. Under such circumstances, insurance plans, including Medicare, must fulfill their obligation to their beneficiaries and cover off-label therapies.

5. “Peer-review” processes, when used to determine whether a drug will be covered for off-label use, must employ reviewing physicians who are true peers with the prescribing provider, with credentials and expertise relevant to the case at hand.

6. Insurance companies and other overarching agencies should not apply penalties nor attempt to recoup payment for therapies administered in good faith, even when prescribed off-label.

BACKGROUND:
Prescribing information contained in FDA labels is submitted by manufacturers with new drug applications and provides official descriptions of drugs including but not limited to indications, doses, adverse drug reactions, recommendations for use in pregnancy and safety information for patients. This information is meant to inform prescribers and patients about the safe and effective use of therapeutic agents. FDA labels are written so as to be devoid of explicit or implied claims of efficacy or suggestions for use in circumstances where safety or efficacy data are not robust or have not been reviewed by the FDA.

FDA regulations governing the content and format of prescription drug labeling were updated in January 2006 (Code of Federal Regulations Title 21). These rules do not limit the use of labeled products to indications described in the label. Indeed, current FDA guidance explicitly directs physicians to use “legally available drugs, biologics and devices according to their best knowledge and judgment.” The FDA recognizes off-label use of products as appropriate and elaborates by clarifying that “If physicians use a product for an indication not in the approved labelling, they have the responsibility to be well-informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and affects.” (1)

This issue is especially germane to the care of children. As outlined in The American Academy of Pediatrics Policy Statement on the Off Label Use of Drugs in Children (2), “for the pediatric population, gold standard clinical trials are often not available, so practitioners must rely on either less definitive information, such as expert opinion for the age group that they are treating, or use evidence from a different population to guide practice. This situation is especially true when treating rare diseases or sparse populations such as neonate…. They go on to correctly state that “off-label use is neither incorrect nor investigational if based on sound scientific evidence, expert medical judgment, or published literature.” And furthermore “less expensive therapeutic alternatives considered appropriate for adults should not automatically be considered appropriate first-line treatment in children.”

Without off-label use of prescription products, the therapeutic options for many rheumatologic conditions, even relatively common ones, are vanishingly few. Indeed, the standard of care for many patients with rheumatologic diseases requires the off-label use of prescription products. Some examples below illustrate this point.

- Systemic sclerosis affects approximately 75,000 to 100,000 people in the U.S. and has the single highest mortality rate of any autoimmune rheumatic disease (3,4). In spite of the grave threat posed by this diagnosis, there is no FDA-approved therapy for systemic sclerosis. Thus, rheumatologists and other providers routinely and appropriately recommend the off-label use of a range of therapies including cyclophosphamide, mycophenolate mofetil, and methotrexate.

- Rheumatologists routinely use infliximab and/or adalimumab (tumor necrosis factor inhibitors (TNF inhibitors)) to treat uveitis that is idiopathic or secondary to underlying diseases such as juvenile inflammatory arthritis, sarcoidosis, tubulointerstitial nephritis and uveitis syndrome, and Behcet’s disease. Neither drug is FDA-approved for the treatment of uveitis. Patients, especially children, who have progression or persistence of
ocular inflammation in spite of topical ophthalmic medications and/or systemic medications such as methotrexate are at high risk of developing cataracts, glaucoma, band keratopathy, and blindness. Prompt initiation of a TNF inhibitor, therefore, is paramount. There are numerous case reports, case series, and systematic reviews that demonstrate the efficacy of infliximab and adalimumab for recalcitrant uveitis (5-12).

- There are currently no FDA-approved medications for the treatment of juvenile dermatomyositis (JDM). Patients with moderate to severe or refractory disease often benefit from intravenous immunoglobulin (IVIG). Unfortunately, randomized clinical trials testing IVIG in children with JDM have not been reported. However, retrospective studies suggest efficacy of IVIG in JDM (13) and the Childhood Arthritis & Rheumatology Research Alliance has published two consensus treatment protocols for moderate JDM, which include IVIG treatment arms (14,15).

- Methotrexate is a first-line agent and the standard of care for a large number of rheumatologic conditions but is only FDA approved for three (rheumatoid arthritis, psoriasis and polyarticular juvenile rheumatoid arthritis).

- According to the National Organization for Rare Disorders, despite the passage of the Orphan Drug Act of 1983, the vast majority of rare disorders do not have an FDA-approved medication. Thus, providers must treat over 90 percent of these patients off-label (16).

- Colchicine has been used in the US as effective therapy for gout for over a century, but gained FDA approval only in 2009.

Despite the evidence and broad clinical experience supporting the use of such agents, and in spite of a lack of alternatives, insurance coverage for many such drugs is frequently denied. The justification put forth for these denials is that the drugs are not approved by the FDA for the intended indication although they are approved for other indications. The mechanism for such denials often involves a “peer-review” process wherein a medical doctor, who is paid by the insurance company, reviews the case, sometimes engaging directly with the prescriber, and recommends whether or not to approve coverage for the therapy. When peer-review processes are employed, it is paramount that the reviewing physician be a true peer of the prescriber, with credentials and expertise relevant to the case at hand, and not a generalist or a (sub-)specialist from another field. For example, appropriate review of pediatric rheumatology cases requires a pediatric rheumatologist.

Many drugs, especially “orphan” drugs used for rare diseases and drugs used in pediatrics, will never be taken by manufacturers to the FDA for approval because the costs associated with doing so relative to the income from the drug is prohibitive. The patients with these diseases must not be deprived access to effective therapy for such reasons.

FDA labels are further limited by the fact that the information and advice they contain is not updated as quickly as advances in accepted medical practice. By design, post-marketing surveillance and widespread, real-world experience with new drugs do not begin until after the
FDA labels are approved. Unfortunately, new information is often slow to be incorporated. For example, dose acceleration of TNF inhibitors is widely accepted as medically necessary and effective for a subset of patients with psoriatic arthritis and inflammatory bowel disease-associated arthritis, but the use of higher doses is not addressed in the FDA labels for all of these agents. Thus, insurance coverage for the higher doses is frequently denied. Another example: TNF inhibitors are emerging as one of the safest alternatives for patients with rheumatoid arthritis during pregnancy, but this nuance of care is not reflected in FDA labels. Finally, some drugs with altered formulations and routes of administration are used in a medically appropriate fashion for new indications before FDA labels can be updated. In these and similar circumstances, denial of coverage based on FDA labels stands in stark opposition to FDA guidance that physicians base the use of legally available drugs “according to their best knowledge and judgement”.

Even government payers deny and delay coverage for drugs explicitly on the grounds that the drugs are not FDA approved for a particular indication. Medicare Part D, for example, requires beneficiaries to seek the support of the prescribing provider, traverse layers of review, and submit proof in support of the use of off-label drugs from one of three officially recognized drug compendia. Access to these compendia is limited and costly and their navigation is beyond most laypeople (having been written for medical practitioners and in highly technical language.) (42 U.S.C. §1395w-102(e)(4)(B)). These practices delay and limit access to appropriate therapy and thereby harm patients.

Finally, when the prescribing provider’s decision to prescribe a drug for an off-label indication is medically necessary and in the patient’s best interests, it is inappropriate for insurance companies or other overarching agencies to apply penalties or attempt to recoup payment for therapies administered in good faith.

In summary, the ACR agrees with the FDA’s acknowledgement, support and recommendation for the use of off-label therapies when appropriate and medically necessary. The ACR recognizes that patients who rely on off-label therapies for rheumatologic conditions, including many diseases for which no FDA-approved therapies are available, face tremendous hurdles and delays in gaining access to treatments due to the inappropriate use of restrictions in coverage based on FDA labeling. The ACR recommends such practices be abandoned and supports consistent policies that allow fair access to medically appropriate drugs both on- and off-label.

REFERENCES:


3. ACR website
https://www.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Scleroderma_(also_known_as_systemic_sclerosis). (Last accessed: June 3, 2015)


