April 29, 2011

Jeffrey Kang, MD, MPH
Chief Medical Officer, CIGNA Corporation
CIGNA Corporate Offices
900 Cottage Grove Rd.
Bloomfield, CT 06002

Dear Dr Kang:

The American Academy of Pediatrics (AAP) and the Arthritis Foundation (AF), oppose Cigna's new policy on the standard requirements for the use of Infliximab in the treatment of children and young adults with rheumatic and autoimmune diseases. This policy as currently written will have a significant and harmful effect on the health of the children under our care.

1. **Care decisions should be made by a skilled and appropriately certified physician**. Pediatric Rheumatologists' require a minimum six years of additional training after completion of medical school to care for children with complex and often ill defined medical conditions. The decisions of a physician should not be restricted by an arbitrary policy that will restrict access to a medication already used as a standard of care in pediatric rheumatology. This policy essentially undermines the physician–patient relationship and leaves Cigna free of liabilities.

2. **Current Standard of Care**:
   Infliximab is currently used in pediatric rheumatic diseases. There are many published reports of effectiveness in up to 26% of JIA patients in the United States using TNF inhibitors.

   2010 ACR abstract [Beukelman T, Xie F, Curtis JR. Usage of TNFα inhibitors for the treatment of juvenile idiopathic arthritis: data from a national U.S. administrative claims database [abstract]. Arthritis Rheum 2010; 62 Suppl 10:S100-1.]: In 2005 through 2008, among JIA patients that newly started anti-TNF therapy 26% (62 of 242) started infliximab. Among JIA patients with uveitis that newly started anti-TNF therapy, 54% (21 of 39) started infliximab.

2011 PRSYM abstract [Ringold S, Beukelman T, Morgan DeWitt E, Natter M, Nigrovic P, Kimura Y. Disease Characteristics and Medication Use in a Multicenter Cohort of Children with Juvenile Idiopathic Arthritis (JIA): Preliminary Analyses from the CARRAnet Registry [abstract]. Submitted]: Among JIA patients who are current users of anti-TNF, about 13% (46 of 347) are receiving infliximab.

3. **Pediatric Rheumatic Diseases are a poorly defined and herterologous group of disorders** that are divided into broad descriptive categories. Currently 300,000 children are estimated to have rheumatic disorders. Current categories of Juvenile Idiopathic Disease (JIA) have been subject to re-definition and a large portion of children,30% or more, do not fit into a standard category. These diseases are not identical to their adult counter parts and there is evidence to suggest that there may be differences in

pathogenesis. Therapeutic response may vary based on environmental exposure, ethnicity and age at onset of disease, and length of time since disease onset. Many children have overlapping and systemic disease features that will affect the choice of treatment. The poor outcome and the increased morbidity and mortality of children with these diseases are established and most children will enter into their adult years with active disease. Other children have co-morbid conditions that further complicate disease management.

4. **Evidence Base in Comparing TNF inhibitors in the treatment of Childhood Rheumatic Diseases.** FDA review of Infliximab involved one study enrolling 122 children with restricted indications http://onlinelibrary.wiley.com/doi/10.1002/art.22838/abstract Because of unblinding at one site and subsequent removal of 4 study patients, the study was under powered to detect any difference in efficacy for the primary end point. The study sponsor was fully forth coming about the limitation of the study but was not required by the FDA to repeat or improve on design flaws. At this time there is not enough evidence available for an insurance company to exclude patients from drug coverage. Very little data exist comparing one TNF inhibitor to another the single published study Clinical and Experimental Rheumatology 2011 29 131-39 by Lamot, L, Bukovac et al , does not suggest Infliximab is less effective than Etanercept in JIA.

5. **Prescription coverage restricted to FDA approved indications is not the current standard of care in pediatrics.** Up to 75% of prescriptions written for children are for non-FDA approved indications. Any attempt to enforce such a restriction would be opposed by the AAP and the Arthritis Foundation.

American Academy of Pediatrics, Committee on Drugs. Unapproved Uses of Approved Drugs: The Physician, the Package Insert, and the Food and Drug Administration Subject Review. Pediatrics 1996;98:143-145. http://aappolicy.aappublications.org/cgi/reprint/pediatrics;98/1/143.pdf

Pediatric Drug Labeling: Improving the Safety and Efficacy of Pediatric Therapies. JAMA 2003; 290:905-911.

6. **Special Needs in Children / Behavioral / Cultural and Family Considerations**
The AAP and the Arthritis Foundation support policy that allows physicians to respect family preferences or family limitations. Our families are under considerable stress dealing with a chronically ill child. We have families who are unable to administer subcutaneous injections because the child might be needle phobic or the well documented pain of TNF injections. We have families who prefer infusions because it helps them remain on schedule and compliant, and there are families who do not have reliable refrigeration. Some families restrict use of medications based on media reports or other family members who have experienced side effects. We believe that the family and physician should be allowed to choose the appropriate treatment option based all pertinent considerations. Pediatricians are ultimately responsible for making sure the child receives appropriate treatment and that means the parents must be comfortable with

the choices available. Restricting medications and delivery method availability will prevent these families from getting the choices they need to best care for their children.

7. **Dosing issues** – While injectable medications provide significant conveniences for dosing in adults, several of these medications are provided in one-dose administration units that are inappropriate for children and difficult-to-impossible to scale to pediatric use. Requiring the use of such medications carries with it significant chances of dosing errors and concomitant problems.

8. **Safety in Pediatric Rheumatology Conditions** – There are safety issues unique to children in using immunosuppressive medication. In addition, the FDA recently put a block box warning on TNF inhibitors for cases of malignancy reported in children. Some complications like Macrophage Activating Syndrome have a much higher prevalence in children. Safety concerns and for children who will be taking these medications for decades –long term safety concerns are paramount in making a treatment decision. Limiting options when there are safety issues may restrict the physician from making a balanced risk assessment, especially for patients with complex and multiple concurrent disease processes.

9. **Responders** Cigna's new policy seems to have no provision for a pediatric patient already having an excellent clinical response to these medications.

10. **Uveititis: Strong Evidence to Support Pediatric treatment and allow the physician to decide indication for use.**
We recommend that coverage also be added for patients (children or adults) with iritis/uveitis that is not adequately controlled with methotrexate.

    The specific diagnostic codes include all the codes the cover pediatric uveitic diseases that may be treated with Infliximab:

    363.20
    363.21
    364.00
    364.01
    364.02
    364.03
    364.04
    364.10

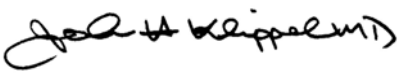
    References supporting the use of Infliximab include the following:
1. Suhler, EB, Smith, JR, Giles, TR et al. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. Arch Ophthalmol 2009;127:819-822.
2. Ardoin, SP, Kredich, D, Rabinovich, E et al. Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. American Journal of Ophthalmology 2007;144:844-849.
3. Sobrin, L, Kim, EC, Christen, W et al. Infliximab therapy for the treatment of refractory ocular inflammatory disease. Archives of Ophthalmology 2007;125:895-900.

Children are using TNF inhibitors in significant numbers, and pediatric rheumatologists have become familiar with their uses and limits. There are multiple factors that need to be considered in choosing the right medication for a child, as there is a tremendous difference between caring for a patient and taking care of a disease. There is no evidence on which to base the proposed policy in children. We would welcome the opportunity to partner with CIGNA and the American College of Rheumatology to create a policy for children with rheumatic conditions. We have a shared goal of providing quality care and preventing disability. We hope that companies like Cigna will value the insights and experience of the pediatric rheumatology community. The AAP Section on Rheumatology Executive Committee will be meeting on May 14, 2011 and you and your staff are cordially invited to discuss this further via conference call. For information regarding the meeting please contact Laura Laskosz, AAP staff manager for the AAP Section on Rheumatology at llaskosz@aap.org.

The American Academy of Pediatrics represents 60,000 pediatricians and pediatric subspecialists.

The Arthritis Foundation represents 50 million adults and 300,000 children living with arthritis.

Sincerely,



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American Academy of Pediatrics
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OMB/ll

cc: Douglas Hadley, MD
Greg Lizer, MD