NATIONAL INFUSION CENTER ASSOCIATION

December 14, 2015

Jim Carlson, PharmD
Vice President, Pharmacy and Clinical Services
OmedaRx
100 Southwest Market Street
Portland, OR 97207

RE: Step Therapy Policy

Dear Mr. Carlson:

The National Infusion Center Association (NICA) was recently contacted by our concerned partners in Washington regarding biologic medication claim rejection due to a Step Therapy policy for Regence BlueShield of Washington plans. It is our understanding that Regence BlueShield has implemented Step Therapy or "Fail First" requirements for one or more biological injectable/infusible medications.

We verified these Step Therapy policies in the *RegenceRx Medication Policy Manuals* for Actemra, Cimzia, Entyvio, and Orencia. **As a result, we are reaching out in hopes of opening an important dialogue concerning these prior authorization methodologies that include Step Therapy or "Fail First" requirements for certain IV/injectable biologic medications.**

We wish to facilitate a conversation between our partners and Regence decision-makers to discuss the patient access impact of these specific Step Therapy policies.

NICA understands that health care plans have an ongoing need to control formularies and costs related to the growing specialty medication market. Biologics are some of the most innovative and life changing medications developed in the last 15 years. This class of medications brings unique challenges to manufacturers, providers, patients and insurers, including: escalating costs, complex clinical administration, and a difficult reimbursement environment.

It is with these challenges in mind that the NICA has formed criteria for Step Therapy/Fail First policies specific to intravenous and injectable medications and biologics, outlined below in Figure 1.

FIGURE 1: NICA CRITERIA FOR STEP THERAPY REQUIREMENTS

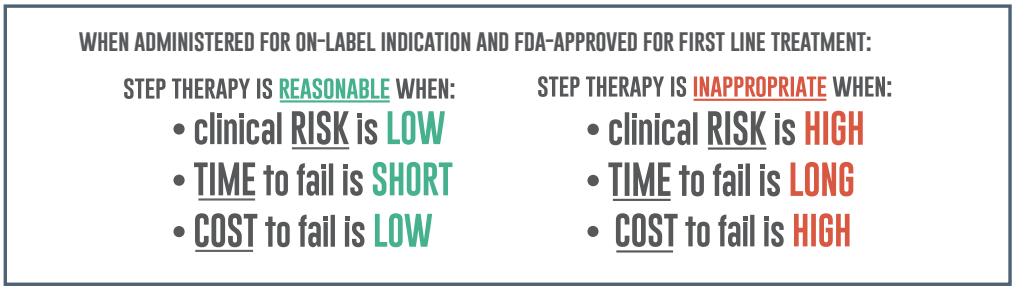

Figure 1 presents a common sense test for Step Therapy policies using NICA criteria for reasonable and inappropriate use of Step Therapy.

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NICA supports responsible access to biologic therapies so providers and patients may safely and more cost-effectively find the best biologic therapy—the one that works. NICA believes that Step Therapy is reasonable in certain circumstances: when the Clinical RISK is LOW, the TIME to fail is SHORT, and the COST to fail is LOW.

REGENCE BLUESHIELD OF WASHINGTON–CURRENT STEP THERAPY REQUIREMENTS

In referencing the published *RegenceRx Medication Policy Manuals* available on the Regence BS website, we noticed that at least four biologics had Step Therapy requirements: Actemra, Cimzia, Entyvio, Orencia. We researched these medications and found that all of them have FDA approval as first-line biologic treatments for their primary indications.[2,4,10] However, according to the *RegenceRx Medication Policy Manuals* for these drugs, they each have at least 1 or 2 failure requirements of a "preferred biologic" which appear to be Enbrel, Humira, and/or Remicade. All of these drugs impacted by Step Therapy requirements are FDA-approved as a first-line indication in the conditions for which there is a Step Therapy requirement. Additionally, several biologics are under varying Step Therapy requirements per condition or per route of administration. The specific language used in the respective *RegenceRx Medication Policy Manual* is outlined below in Table 1.

TABLE 1: STEP THERAPY REQUIREMENTS FOR CERTAIN BIOLOGICS

MEDICATION	STEP THERAPY LANGUAGE
ACTEMRA	RHEUMATOID ARTHRITIS: "… CLINICAL DOCUMENTATION THAT TREATMENT WITH INFLIXIMAB (REMICADE) WAS NOT EFFECTIVE AFTER AT LEAST A 6 TO 12 WEEK TREATMENT COURSE…"
CIMZIA	CROHN'S DISEASE: "… THERE IS CLINICAL DOCUMENTATION THAT ADALIMUMAB (HUMIRA) IS NOT EFFECTIVE AFTER AT LEAST AN INITIAL THREE-DOSE INDUCTION PERIOD UNLESS IT IS NOT TOLERATED." PSORIATIC ARTHRITIS: " … THERE IS A DOCUMENTED MEDICAL REASON WHY ADALIMUMAB (HUMIRA) AND ETANERCEPT (ENBREL) ARE EACH NOT TREATMENT OPTIONS AND THERE IS CLINICAL DOCUMENTATION THAT TREATMENT WITH USTEKINUMAB (STELARA) WAS NOT EFFECTIVE AFTER AT LEAST A 12 WEEK TREATMENT COURSE UNLESS NOT TOLERATED OR CONTRAINDICATED." RHEUMATOID ARTHRITIS: "… THERE IS A DOCUMENTED MEDICAL REASON WHY ADALIMUMAB (HUMIRA) AND ETANERCEPT (ENBREL) ARE EACH NOT TREATMENT OPTIONS."
ENTYVIO	ULCERATIVE COLITIS OR CROHN' DISEASE: "… TREATMENT WITH INFLIXIMAB (REMICADE) AND ADALIBUMAB (HUMIRA) WERE NOT EFFECTIVE AFTER AT LEAST A 12-WEEK TREATMENT COURSE [BOTH INDIVIDUALLY] UNLESS [THE DRUG] WAS NOT TOLERATED OR CONTRAINDICATED."
ORENCIA	RHEUMATOID ARTHRITIS (IV): " … TREATMENT WITH INFLIXIMAB (REMICADE) WAS NOT EFFECTIVE AFTER AT LEAST A 12-WEEK TREATMENT COURSE UNLESS IT WAS NOT TOLERATED OR IS CONTRAINDICATED." RHEUMATOID ARTHRITIS (SC): " … TREATMENTV WITH TWO PREFERRED BIOLOGIC THERAPIES WERE EACH NOT EFFECTIVE AFTER AT LEAST A 12-WEEK TREATMENT COURSE UNLESS IT WAS NOT TOLERATED OR IS CONTRAINDICATED."

SOURCE: *REGENCERX MEDICATION POLICY MANUALS FOR ACTEMRA, ENTYVIO, CIMZIA, AND ORENCIA* (ACCESSED 11/21/2015)

Table 1 outlines the specific Step Therapy language for Actemra, Entyvio, Cimzia and Orencia included in the included in corresponding *Medication Policy Manual.*

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CIMZIA

Additionally, for the treatment of moderate to severely active CD with Cimzia, patients must fail Humira. However, for the treatment of moderate to severely active Rheumatoid Arthritis (RA) with Cimzia, patients are NOT required to fail Humira, but can instead provide a **"documented medical reason why Humira and Enbrel are each not treatment options."** Furthermore, patients with Psoriatic Arthritis (PsA) must provide clinical documentation indicating that Humira and Enbrel are not treatment options, AND documentation of failing Stelara or that it was contraindicated. Cimzia is FDA approved as a first-line indication in patients with moderately to severely active CD, active PsA or RA.[2] Yet there is a Step Therapy requirement for CD patients, but not for RA patients. Additionally, PsA patients must provide documentation that two other drugs are not a treatment option *and* fail a third.

ENTYVIO

In the case of reported Entyvio reimbursement denials due to prior authorization methodologies, we researched this medication and found that it is indicated in biologic-naïve adult patients with moderate to severe Crohn's Disease (CD) or Ulcerative Colitis (UC) as illustrated below in Figure 1.[4,6]

FIGURE 2: ENTYVIO INDICATIONS AND USAGE

ENTYVIO IS AN INTEGRIN RECEPTOR ANTAGONIST INDICATED FOR:

ADULT ULCERATIVE COLITIS (UC):

ADULT PATIENTS WITH MODERATELY TO SEVERELY ACTIVE UC WHO HAVE HAD AN INADEQUATE RESPONSE WITH, LOST RESPONSE TO, OR WERE INTOLERANT TO A TUMOR NECROSIS FACTOR (TNF) BLOCKER OR IMMUNOMODULATOR; OR HAD AN INADEQUATE RESPONSE WITH, WERE INTOLERANT TO, OR DEMONSTRATED DEPENDENCE ON CORTICOSTEROIDS:

- INDUCING AND MAINTAINING CLINICAL RESPONSE
- INDUCING AND MAINTAINING CLINICAL REMISSION
- IMPROVING ENDOSCOPIC APPEARANCE OF THE MUCOSA
- ACHIEVING CORTICOSTEROID-FREE REMISSION

ADULT CROHN'S DISEASE (CD):

ADULT PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CD WHO HAVE HAD AN INADEQUATE RESPONSE WITH, LOST RESPONSE TO, OR WERE INTOLERANT TO A TNF BLOCKER OR IMMUNOMODULATOR; OR HAD AN INADEQUATE RESPONSE WITH, WERE INTOLERANT TO, OR DEMONSTRATED DEPENDENCE ON CORTICOSTEROIDS:

- ACHIEVING CLINICAL RESPONSE
- ACHIEING CLINICAL REMISSION
- ACHIEVING CORTICOSTEROID-FREE REMISSION

SOURCE: *ENTYVIO PACKAGE INSERT* (ACCESSED 11/28/15)

Figure 2 presents the primary indications of usage of Entyvio for the treatment of moderate to severe UC and CD.

The FDA approved Entyvio for first-line treatment of moderate to severe UC or CD in adult patients after failing an anti-TNF, an immunomodulatory OR corticosteroids.[4,6] The FDA does not require failure of an anti-TNF drug before pursuing Entyvio treatment. Therefore, when a physician and patient collectively decide that this drug is the best treatment option, they should be able to proceed with the physician-recommended therapy. However, according to Regence BlueShield (WA) Step Therapy requirements, at least 1 or 2 TNF inhibitors must be failed in order to access Entyvio.

ORENCIA

Patients must fail Remicade for authorization to pursue intravenous Orencia for the treatment of moderately to severely active RA. However, these patients must fail "two preferred biologic therapies... unless not tolerated or contraindicated" for authorization to pursue subcutaneous Orencia. Orencia is FDA approved as a first-line intravenous or subcutaneous treatment for patients with moderately to severely active RA. Yet, there is a single Step Therapy requirement for intravenous administration and double Step Therapy for subcutaneous administration.

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We could not find any scientific literature to support these methodologies which contrast FDA guidelines. Therefore, these prior authorization methodologies for double failure, a single drug across multiple disease states, and a single drug across multiple routes of administration appear unnecessary.

Incongruent with NICA criteria for reasonable step therapy

We understand the need to address the financial challenges of these medications. However, Step Therapy requirements can have significant impact on health outcomes and quality of life when inappropriately implemented. When considering both the NICA Criteria for Step Therapy and Regence BlueShield's own Step Therapy guidelines, we conclude that the current Step Therapy requirements for these drugs are unreasonable and inappropriate. The current guidelines fall short in all three of our test criteria for reasonable Step Therapy requirements.

TIME TO FAIL IS LONG

All of the listed first step biologics, for both primary- and secondary-mandated failures, require a LONG time to be considered and documented for failure. The time to failure is at least 3-6 months for Humira and Remicade. For a patient with progressive chronic disease, this time equates to deteriorating health and significantly reduced quality of life. Each day of delayed treatment is often spent in debilitating pain and suffering. Requiring a patient to trial what might be an ineffective or second-choice biologic – as determined by the patient and physician – can allow progression of disease to a state that requires invasive intervention.[5,9,11] **When provider and patient collectively decide that a drug is the best treatment option for their disease, they should be able to proceed with the physician-recommended therapy rather than delay treatment with one or more health plan mandated therapies.**

CLINICAL RISK IS HIGH

All medications, including the preferred biologics, carry an inherent clinical risk that varies between patients. The preferred biologics outlined in the *RegenceRx Medication Policy Manuals* carry FDA Black Box warnings and adverse event profiles that are far from benign (e.g., serious infections, malignancies, and adverse reactions).

We could not locate any head-to-head peer-reviewed evidence where either safety or clinical efficacy for these four biologics (Actemra, Entyvio, Cimzia or Orencia) was demonstrated to be less than that of the "preferred biologics" when used for their FDA-approved indications. We did find evidence which at least suggests that failure of 1 anti-TNF treatment was associated with an increased rate of second anti-TNF discontinuation for the same reason (i.e. primary failure, secondary failure, or intolerance).[7-9] According to a 2010 study, approximately one in three patients with Crohn's disease that fail standard treatment did not respond to anti-TNF drugs and at least half of those that did respond experienced secondary failure within a year.[7] This makes the failure requirement of 2 anti-TNF's via Step Therapy seem less reasonable, wasteful and possibly more harmful.[1,3,7-9] These Step Therapy requirements force healthcare providers and patients to try and fail medication(s) that they have already decided are not the best primary pathway to treat the disease.

It is appropriate for the provider and patient to be responsible for weighing these risks and making a collaborative decision as to which primary treatment protocol to use. **Patients should not be required to expose themselves to these unnecessary clinical risks prior to receiving the treatment they need.**

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COST TO FAIL IS HIGH

We understand that a primary driver of Step Therapy for health care plans is cost management. All of the medications listed in this letter have annual costs in the tens of thousands of dollars. With an average treatment duration of at least 3-6 months to document failure, the cost of trying and failing the wrong drug is significant. Double-Step Therapy requirements exponentially increase these costs. In our research we found evidence indicating that the high cost of failing biologic therapy in patients with autoimmune diseases can easily negate any short-term cost savings realized through Step Therapy as a cost management strategy.[4,8-10,13] This cost is not only a burden on the health plan, but also a burden on the patient. Typical cost-sharing on these medications range from the $100's to $1,000's per treatment. **A patient who receives thousands of dollars of medication without therapeutic benefit is a Lose-Lose proposition for everyone.**

CONCLUSION

Using our current understanding of Regence BlueShield's Step Therapy guidelines and existing literature, we conclude that imposing requirements for all patients to try and fail drugs mandated by health plans before pursuing provider-prescribed drugs may significantly delay therapeutic benefit (time to fail is long), increase costs (cost to fail is high) and unnecessarily expose patients to additional risk (clinical risk to fail is high). **Therefore, we find it impractical, wasteful, and possibly even harmful that accessing these physician-prescribed biologics would require failing one or more health plan-prescribed biologics.**

NICA agrees with many of our partner patient and disease advocacy organizations and believes that the decision as to which biological therapy is best suited for a particular patient should be a collaborative determination by healthcare providers and patients on an individual patient basis, not a blanket requirement for all patients implemented by the health plan. **NICA supports responsible access to biologics so providers and patients can safely, quickly, and more cost-effectively find the best biologic therapy—the one that works.**

Placing the utmost importance on improving health outcomes and optimizing quality of life in the safest, most economical way, NICA respectfully requests that Regence BlueShield reconsider its decision to implement Step Therapy policy for these biologics. In addition, on behalf of patients and our provider partners, we are requesting the opportunity to review and discuss these policies in the interest of identifying an all-win solution for Regence BS, providers and patients.

Thank you for your time and consideration,

Brian Nyquist, MPH Executive Director
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CC: Jared Short — President, Regence Health Insurance Services
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