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# Policy Evaluation: Biologics for RA, Psoriasis, or Crohn's Disease

**Research Questions:**

- What proportion of biologic claims were for preferred drugs, both before and after the prior authorization (PA) was implemented?
- What diagnoses are associated with specific biologic drugs?
- What proportion of new patients on biologics had evidence of previous conventional therapy since implementation of the clinical PA in February 2013 and compared to before the PA?
- Is there evidence of interruption of therapy or an unintended increase in all cause hospitalizations or emergency department (ED) visits after the PA policy?

**Conclusions:**

- Overall, there was an increased trend in the number of patients using a biologic prior to the PA policy and a decrease trend after implementation of the PA policy. Most pharmacy claims (79%) were for the preferred products adalimumab and etanercept, both before and after policy implementation due to the function of the preferred drug list (PDL).
- Most patients had an indication that approved by the U.S. Food and Drug Administration (FDA) and funded by OHP (77.6% prior to PA implementation and 76.6% after PA implementation), with no significant difference seen between the control and study groups. The most common indications associated with pharmacy claims were rheumatoid arthritis, Crohn's disease, and chronic plaque psoriasis. Common indications associated with medical claims were rheumatoid arthritis, Crohn's disease, and multiple sclerosis. In patients with no associated diagnoses, most had antineoplastic immunotherapy, malignant neoplasm, or lymphoma with a medical claim.
- Use of disease-modifying antirheumatic drug (DMARD) therapy prior to a pharmacy claim for a biologic was low, with similar rates before (45%) and after (47%) policy implementation. A limitation of this assessment is the lack of PA for preferred products, which are the majority of pharmacy claims. Even fewer patients (13%) with medical claims had evidence of prior DMARD therapy, as medical claims have not required a PA up to this point.
- There was insufficient evidence in patients without PA requests that delay or interruption of biologic therapy was related to hospitalization or ED visits; however, this evaluation was not designed to determine an association with certainty.
- The overall small number of claims for biologics makes it difficult to draw strong conclusions from the data.

**Recommandations:**

- Continue to PA non-preferred biologics. Expand current PA to medical claims for biologic agents with auto-approval for cancer and multiple sclerosis indications.
- Require a PA on preferred biologics to promote the appropriate use of DMARD therapy prior to biologic therapy.
- After the biologics class update is completed by the OHSU Drug Effectiveness Review Project (DERP) in June 2016, a re-evaluation of the Biologics PA is needed to promote appropriate use of DMARDs prior to use of preferred or non-preferred biologics.

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**Background:**
The use of biologic agents for treatment of Rheumatoid Arthritis (RA), Crohn's disease, and Psoriasis is rapidly expanding.[1-3] Biologics work by selectively inhibiting the inflammatory pathways and are used in the treatment of a variety of immunologic and inflammatory diseases. Due to the complex pathogenesis of inflammatory diseases, agents from several classes of medications are used to control and maintain the symptoms. While literature strongly supports biologics for treating inflammatory diseases, the high cost and adverse effects of these agents are major concerns. There is not yet a standardized guide for medication selection and the choice of initial biologic therapy is largely based on prescriber preference.[1,4]

The OHP implemented PA criteria only for the use of non-preferred biologics for pharmacy claims on February 21, 2013 (Appendix 1). Medical claims do not currently require PA. The goal of the policy is to 1) limit the use of non-preferred biologics to indications where there was evidence to support efficacy, 2) limit use of these agents to patients who are intolerant to preferred nonbiologic DMARD therapy, and 3) promote use of high value biologics. Prior to the policy update in 2013, non-preferred products required PA to ensure use was for a funded condition. This policy added a step therapy requirement of failure or contraindication to the first-line DMARD therapy before use of a non-preferred biologic agent because there was evidence of off-label use in the OHP population and most patients did not utilize DMARD therapy before initiating a biologic[5]. Step therapy with a DMARD is supported by clinical guidelines and clinical trials. [5] Currently, only non-preferred products on the preferred drug list (PDL) require PA while the two preferred agents (adalimumab and etanercept) are available without restriction. Table 1 lists the currently available biologic agents.

Drug policies have not been formally evaluated for efficacy or unintended harm and published in the medical literature. Thirty-two state Medicaid programs require PA for one or more biologic agent but there is wide variation in specific clinical criteria which makes it difficult to evaluate the impact of PAs on utilization, patient outcomes and cost.[1]

Table 1: FDA-approved Biologics and Supported Indications.

| **Generic** | **Brand** | **Pharmacologic Category** | **Indication** | **Route** |
|---|---|---|---|---|
| Abatacept | Orencia® | Monoclonal antibody | RA, juvenile RA, juvenile idiopathic arthritis | Subcutaneous<br>Intravenous |
| Adalimumab | Humira® | TNF-Inhibitors | RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, CD, plaque psoriasis, UC, hiddradenitis suppurativa | Subcutaneous |
| Anakinra | Kineret® | IL-1 blockers | RA, neonatal-onset multisystem inflammatory disease | Subcutaneous |
| Apremilast | Otezla® | PDE4-Inhibitor | Psoriatic arthritis, plaque psoriasis | Oral |
| Certolizumab | Cimzia® | TNF-Inhibitors | RA, CD, psoriatic arthritis, ankylosing spondylitis | Subcutaneous |

| | | | | |
|---|---|---|---|---|
| Etanercept | Enbrel® | TNF-Inhibitors | RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis | Subcutaneous |
| Golimumab | Simponi® | TNF-Inhibitors | RA, psoriatic arthritis, ankylosing spondylitis, UC | Subcutaneous<br>Intravenous |
| Infliximab | Remicade® | TNF-Inhibitors | RA, CD, psoriatic arthritis, ankylosing spondylitis, UC, plaque psoriasis | Intravenous |
| Natalizumab | Tysabri® | monoclonal antibody | CD, Multiple sclerosis, | Intravenous |
| Rituximab | Rituxan® | monoclonal antibody | RA, CLL, Wegnener granulomatosis, Microscopic polyangitis, non-Hodgkin lymphoma | Intravenous |
| Secukinumab | Cosentyx® | monoclonal antibody | Plaque psoriasis | Subcutaneous |
| Tocilizumab | Actemra® | monoclonal antibody | RA, juvenile idiopathic arthritis | Subcutaneous<br>Intravenous |
| Tofacitinib | Xeljanz® | JAK Inhibitor | RA | Oral |
| Ustekinumab | Stelara® | IL-inhibitor | Plaque psoriasis, psoriatic arthritis | Subcutaneous |
| Vedolizumab | Entyvio® | monoclonal antibody | CD, UC | Intravenous |
| Abbreviations: CD = Crohn's Disease; CLL= chronic lymphocytic leukemia; IL = interleukin; JAK = Janus Kinase Inhibitor; RA = rheumatoid arthritis; TNF = tumor necrosis factor; UC=ulcerative colitis. | | | | |

Therapy for rheumatoid arthritis includes symptom relief with nonsteroidal anti-inflammatory drugs, corticosteroids and other treatments for pain. Oral DMARDs are recommended as first-line therapy (methotrexate, leflunomide, sulfasalazine, etc.). Maximal efficacy of DMARD therapy will not be seen before 6 months in many patients.[6] The American College of Rheumatology (ACR) 2015 guidelines (for early rheumatoid arthritis <6months), recommends monotherapy (methotrexate is preferred, but may also be leflunomide, sulfasalazine, hydroxychloroquine) initially, then biologics with or without MTX.[7] For established rheumatoid arthritis (>6 months), ACR recommends biologics if disease activity is moderate or high after initial DMARD monotherapy or combination therapy. Under the OHP PA policy, use of biologics can be approved if a patient completed a trial that resulted in an inadequate response to DMARDs for 6 months or longer or if the patient has an intolerance or contraindication to conventional therapy. There is no evidence of any conclusive difference in disease activity between biologic agents in the treatment of RA; although there is high quality evidence for the use of TNF inhibitors, abatacept and tocilizumab. Tofacitinib may be considered if treatment with biologic DMARDs fails.

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Therapies for chronic plaque psoriasis include high potency topical corticosteroids, systemic therapy (cyclosporine, methotrexate, acitretin), phototherapy and biologic agents. The American Academy of Dermatology (2009) Guideline recommends that corticosteroids, vitamin D analogues or systemic agents (methotrexate and cyclosporin) are tried as first line therapy and biologic agents to be considered if the first line therapy failed.[8] OHP PA policy is consistent with the AAD guidelines which recommend the use of biologics after the standard therapy of high-potency topical corticosteroids and systemic agents (cyclosporine, methotrexate, or acitretin) have failed.

Psoriatic arthritis (PsA) is an inflammatory arthritis. The goal of therapy is to suppress joint, tendon and entheseal inflammation and to improve skin condition.. Scottish Intercollegiate Guidelines Network guidelines (2010) recommend use of NSAIDs for short-term relief and DMARDs (sulfasalazine, leflunomide, methotrexate, cyclosporine) as the first line therapy for 3 months.[9] If 3 months therapy with DMARDs does not improve the symptoms or if the medications are not well tolerated, then biologic agents should be considered. OHP PA criteria is consistent with SIGN guideline recommendations. There is evidence of no difference in efficacy between adalimumab, etanercept and infliximab for the treatment of PsA.

Ankylosing spondylitis is a chronic inflammatory arthritis with involvement of the spine and sacroiliac joint. Therapies include TNF inhibitors and NSAIDs. NSAIDs are considered first-line drug treatment for pain and stiffness. Biologic agents are recommended for patients with persistently high disease activity despite conventional therapy.[10] Evidence suggests similar efficacy between adalimumab, etanercept and infliximab.[11] The National Institute for Clinical Excellence (2008) recommends that at least two NSAIDs should be tried first, and then biologic agents should be considered.[12] Recent ACR guidelines defines that a lack of response or intolerance to at least 2 different NSAIDs over 1 month, or incomplete responses to at least 2 different NSAIDs over 2 months, would be adequate trials with which to judge a NSAID response.[13]

Crohn's disease is a type of inflammatory bowel disease characterized by chronic full-thickness inflammation that can occur anywhere in the gastrointestinal tract, but most often the small bowel and colon.[3] Approved biologics are infliximab, adalimumab, natalizumab, and vedolizumab. Clinical practice guidelines for Crohn's disease recommend taking into account the disease location, severity, complications, and extraintestinal manifestations when choosing a treatment strategy. [3] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission). [15] Some experts believe that patients have better long-term outcomes taking immunomodulators and biologics early ("top-down therapy"), as opposed to taking them after prolonged steroid use ("step-up therapy") and there is controversy over which method is more effective and currently the step-up strategy remains standard of care. Order of medications from top down is biologics, immunomodulators, corticosteroids, and aminosalicylates. [3] A recent randomized controlled trial compared conventional step therapy to early combined immunosuppression therapy with a TNF inhibitor (top-down therapy) and found no significant benefit in remission rates compared to conventional therapy with a lower rate of major adverse outcomes.[14] The American Gastroenterological Association strongly recommends induction with an anti-TNF drug in patients who have moderately severe CD despite standard therapies, and to maintain corticosteroid or anti-TNF induced remission.[16] NICE guidelines recommend TNF-alpha inhibitors for induction, but only after conventional therapy steroids, azathioprine or mercaptopurine, and should only be used for maintenance if there is clear evidence of active disease.[15]

Ulcerative Colitis (UC) is an inflammatory bowel disease and presents as a shallow, continuous inflammation of the colon.[17] Treatment for ulcerative colitis aims to relieve symptoms during a flare-up and then to maintain remission.[18] Infliximab is recommended by the NICE guidelines as an induction option for acute exacerbations of severely active UC only in patients in whom cyclosporine is contraindicated or clinically inappropriate.[19] The American College of Gastroenterology (ACG) and the NICE Guidelines recommend the use of biologic agents (infliximab, adalimumab and golimumab) as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and

mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.[17,18] In a recent update, the NICE also recommends vedolizumab.[20] Continuation of these agents is only recommended if there is clear evidence of response. [17,18] OHP PA policy is consistent with guideline recommendations, as under their policy, biologic agents are approved for up to 1 year if the patient had a trial resulting in inadequate response to conventional therapy, or has an intolerance or contraindication to conventional therapy.

Possible adverse effects of biologics include increased risk for lymphomas, cervical cancer, or other cancers, as well as increases risk for infections such as tuberculosis or other serious infections. Infusion and injection-site reactions, increased risk for bone fractures, and decreased height and weight in children, have also been associated with use of biologics. The long-term safety of these treatments remains unknown.[3]

The goal of this policy evaluation is to determine the impact of the PA on promoting use of high-value, preferred biologic agents and limiting use of non-preferred agents for supported indications in patients unable to use preferred products.

**Methods:**

Unique patients with a paid FFS pharmacy claim or paid FFS medical claim for any biologic (Appendix 2) from February 2011 through February 2015 were counted by month and plotted in Figure 1.

A pre- and post- observational cohort was constructed to evaluate the policy. Patients were included if they were newly started on any biologic. FFS pharmacy claims were identified by NDC (Appendix 2). FFS medical claims were identified by procedure codes (Appendix 3).

The first biologic claim in the study period with no other biologic claim in the 100 days prior (including coordinated care organization claims) is referred to as the "index claim." Patients with a paid index claim from February 2011 through January 2013 were defined as the *control* group; patients with a paid or denied index claim from March 2013 through February 2015 were defined as the *study* group. Denied pharmacy claims had EOB code 1056 or 1059 on the claim which indicated that PA was required when EOB code 2017 ("patient enrolled in managed care organization") was not simultaneously present. Each group was further sub-divided into the type of claim that marked the index event: paid pharmacy; denied pharmacy; or paid medical.

Patients from both groups were excluded if they had less than 75% eligible days during the 12 months prior to the index claim. Patients with Medicare Part D coverage (BMM, BMD, MED and MND benefit packages) were also excluded. These exclusions were made to minimize missing claim data for patients.

In addition to basic demographics, the presence of a DMARD claim in the year prior to the index claim was flagged. "Year prior" includes the year prior to, and including, the index date. DMARD drugs and codes are defined in Appendix 4.

Patients were categorized by generic drug name of their index event and by the presence of diagnostic codes in the year prior to their index claim. Patients were grouped into mutually-exclusive diagnostic categories: 1) FDA-approved and OHP-funded; 2) off-label and OHP-funded; 3) unfunded condition; and 4) none of the above.

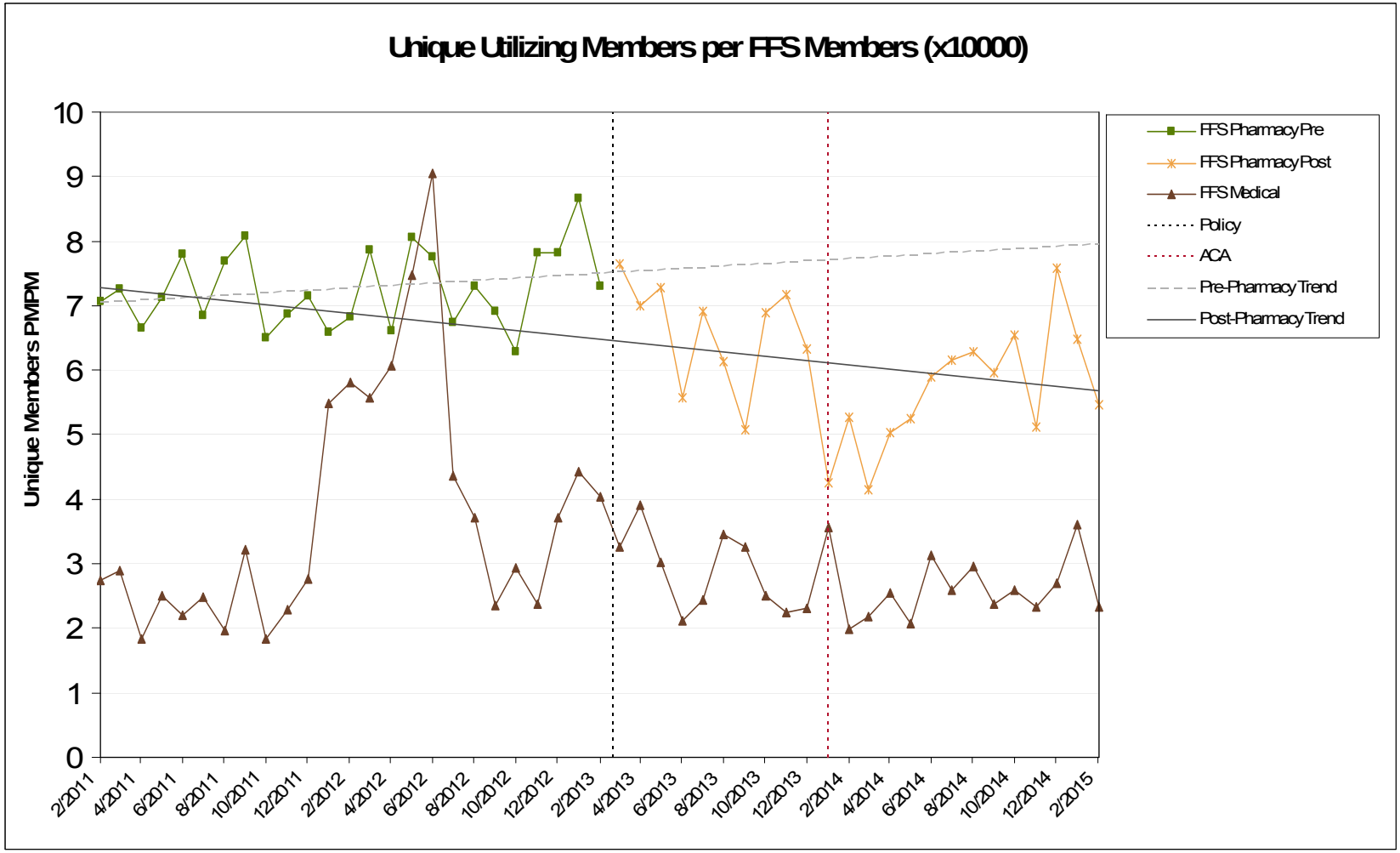
Patients whose index event was a denied pharmacy claim were categorized by final PA disposition: No PA Requested, PA Requested - Approved and PA Requested - Denied. These patients were categorized as to whether they were hospitalized or had an ED encounter for any reason on the day of the index claim or 90 days thereafter.

Patient profiles were reviewed for the following subgroups: 1) patients with a paid pharmacy claim for a non-preferred agent (n=3); 2) patients with an unfunded diagnosis or no diagnosis (n=34) for both pharmacy and medical claims; and 3) patients with no PA requested following a denied pharmacy claim (n=8).

**Results:**

Overall, there was very low use of biologics by FFS OHP patients (<10 patients per PMPM x 10,000). The trend for unique patient biologic use per month, per FFS members times 10,000, before and after the PA was implemented for pharmacy claims, is shown in Figure 1. There was an increased trend in the number of patients using a biologic prior to the PA policy and a decrease trend after implementation of the PA policy. The medical claim trend is flat except for a brief period in 2012. Overall, there was consistently more pharmacy claims than medical claims for biologics.

*Figure 1: unique patient count per month per FFS members x 10,000.*




From February 2011 through February 2015, 113 non-Medicare patients with new-start FFS paid or denied pharmacy claims for biologics, were eligible for the study. An additional 193 patients were eligible with new-start FFS medical claims. Table 2a and 2b contains demographic information for study participants with pharmacy claims and medical claims, respectively. The majority of patients with pharmacy claims were adults, white and female. Prior DMARD use occurred in less than half the patients, both before and after implementation of the PA, with no difference between the study (46.9%) and control (44.9%) groups. In the medical claim group, there was a greater distribution in age of patients after PA implementation, with more pediatric patients included. Patient demographics for medical claims was similar, as most patients were adults, white and female. However, only 12.9% of patients in the medical claim group had evidence of prior DMARD therapy.

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*Table 2a: Demographics; Pharmacy Claims.*

| | Control Group | | | | | | Study Group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **All Index Events** | | *Index Event Paid Claim* | | *Index Event Denied Claim* | | **All Index Events** | | *Index Event Paid Claim* | | *Index Event Denied Claim* | |
| N= | 49 | | 46 | | 3 | | 64 | | 50 | | 14 | |
| Mean age (years) | 37.9 | (6-63) | 38.4 | (6-63) | 29.7 | (19-51) | 39.1 | (4-65) | 39.7 | (16-65) | 34.3 | (4-60) |
| < 6 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 1.6% | 0 | 0.0% | 1 | 7.1% |
| 6-17 | 3 | 6.1% | 3 | 6.5% | 0 | 0.0% | 3 | 4.7% | 1 | 2.0% | 2 | 14.3% |
| ≥ 18 | 46 | 93.9% | 43 | 93.5% | 3 | 100.0% | 60 | 93.8% | 49 | 98.0% | 11 | 78.6% |
| Female | 33 | 67.3% | 30 | 65.2% | 3 | 100.0% | 46 | 71.9% | 36 | 72.0% | 10 | 71.4% |
| White | 37 | 75.5% | 35 | 76.1% | 2 | 66.7% | 41 | 64.1% | 32 | 64.0% | 9 | 64.3% |
| DMARD Year Prior* | 22 | 44.9% | 22 | 47.8% | 0 | 0.0% | 30 | 46.9% | 24 | 48.0% | 6 | 42.9% |

*Table 2b: Demographics; Medical Claims.*

| | Control Group | | Study Group | |
|---|---|---|---|---|
| | **Index Event Paid Claim** | | **Index Event Paid Claim** | |
| N= | 128 | | 65 | |
| Mean age (years) | 46.0 | (10-91) | 40.1 | (2-82) |
| < 6 | 0 | 0.0% | 2 | 3.1% |
| 6-17 | 7 | 5.5% | 9 | 13.8% |
| ≥ 18 | 121 | 94.5% | 54 | 83.1% |
| Female | 83 | 64.8% | 42 | 64.6% |
| White | 106 | 82.8% | 50 | 76.9% |
| DMARD Year Prior* | 16 | 12.5% | 9 | 13.8% |

Table 3a and 3b lists the utilization of specific biologic agents (preferred and non-preferred) based on pharmacy claims (Table 3a) or medical claims (Table 3b). The majority of pharmacy claims were for preferred products, with 86% utilization of preferred agents prior to PA implementation and 76% after the PA was implemented. Certolizumab and infliximab were the most utilized non-preferred agents, but with very low utilization overall. All of the 14 denied claims after the PA was implemented were for non-preferred agents. There were 3 paid claims for non-preferred agents in the study group, but for reasons unclear. Further review of these patient profiles found that two of the three claims were appropriate based on PA criteria. The third claim was not appropriate as there was no evidence of a previous trial of a preferred biologic, and there was no reason for not using a preferred agent. Table 2b displays the use of biologic agents based on medical claims. The three most utilized biologic agents were (infliximab, rituximab, and natalizumab) are all non-preferred agents.

*Table 3a: Biologic Drug Utilization; Pharmacy claims.*

| | **Control Group** | | | | | | **Study Group** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **All Index Events** | | *Index Event Paid Claim* | | *Index Event Denied Claim* | | **All Index Events** | | *Index Event Paid Claim* | | *Index Event Denied Claim* | |
| N= | **49** | | 46 | | 3 | | **64** | | 50 | | 14 | |
| **Preferred** | **42** | **85.7%** | 42 | 85.7% | 0 | 0.0% | **47** | **73.4%** | 47 | 73.4% | 0 | 0.0% |
| Adalimumab | 31 | 63.3% | 31 | 63.3% | | 0.0% | 30 | 46.9% | 30 | 46.9% | | 0.0% |
| Etanercept | 11 | 22.4% | 11 | 22.4% | | 0.0% | 17 | 26.6% | 17 | 26.6% | | 0.0% |
| **Non-Preferred** | **7** | **14.3%** | 4 | 8.2% | 3 | 6.1% | **17** | **26.6%** | 3 | 4.7% | 14 | 21.9% |
| Abatacept | 1 | 2.0% | 1 | 2.0% | | 0.0% | 3 | 4.7% | | 0.0% | 3 | 6.0% |
| Anakinra | | 0.0% | | 0.0% | | 0.0% | 1 | 1.6% | | 0.0% | 1 | 2.0% |
| Apremilast | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Certolizumab | 2 | 4.1% | | 0.0% | 2 | 4.1% | 4 | 6.3% | 1 | 1.6% | 3 | 6.0% |
| Golimumab | 1 | 2.0% | | 0.0% | 1 | 2.0% | | 0.0% | | 0.0% | | 0.0% |
| Infliximab | 2 | 4.1% | 2 | 4.1% | | 0.0% | 4 | 6.3% | | 0.0% | 4 | 8.0% |
| Natalizumab | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Rituximab | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Secukinumab | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Tocilizumab | | 0.0% | | 0.0% | | 0.0% | 1 | 1.6% | 1 | 1.6% | | 0.0% |
| Tofacitinib | | 0.0% | | 0.0% | | 0.0% | 3 | 4.7% | 1 | 1.6% | 2 | 4.0% |
| Ustekinumab | 1 | 2.0% | 1 | 2.0% | | 0.0% | 1 | 1.6% | | 0.0% | 1 | 2.0% |
| Vedolizumab | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |

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*Table 3b: Biologic Drug Utilization; Medical Claims.*

| | Control Group | | Study Group | |
|---|---|---|---|---|
| | Index Event Paid Claim | | Index Event Paid Claim | |
| N= | 128 | | 65 | |
| **Preferred** | | | | |
| Adalimumab | 1 | 0.8% | | 0.0% |
| Etanercept | | 0.0% | | 0.0% |
| **Non-Preferred** | | | | |
| Abatacept | 7 | 5.5% | 5 | 7.7% |
| Anakinra | | 0.0% | | 0.0% |
| Apremilast | | 0.0% | | 0.0% |
| Certolizumab | | 0.0% | | 0.0% |
| Golimumab | | 0.0% | | 0.0% |
| Infliximab | 68 | 53.1% | 34 | 52.3% |
| Natalizumab | 16 | 12.5% | 6 | 9.2% |
| Rituximab | 29 | 22.7% | 15 | 23.1% |
| Secukinumab | | 0.0% | | 0.0% |
| Tocilizumab | 7 | 5.5% | 4 | 6.2% |
| Tofacitinib | | 0.0% | | 0.0% |
| Ustekinumab | | 0.0% | 1 | 1.5% |
| Vedolizumab | | 0.0% | | 0.0% |

Table 4a and 4b displays the associated indications for biologics from the pharmacy and medical claims. The majority of patients in the pharmacy claim group had a condition that was both FDA approved and funded (77.6% in the control group and 76.6% in the study group). The most common indications were rheumatoid arthritis, Crohn's disease, and chronic plaque psoriasis. There were a significant number of patients (22%) who had none of the conditions. These profiles were manually reviewed and while all of these claims were for preferred biologics, there were no appropriate indications recorded. Additionally, the majority of these profiles did not list any previous DMARD therapy. Similarly, the majority of patients with medical claims both before (77.3%) and after (70.8%) the policy had claims record of an FDA approved indication. The three most common indications were rheumatoid arthritis, Crohn's disease, and multiple sclerosis. Profile review showed that for the patients with no associated diagnoses, most patients had antineoplastic immunotherapy, malignant neoplasm, or lymphoma. Other potentially associated indications were unclear, but may have included anemia, osteoporosis, and juvenile RA. There was almost no indication of use for off-label or non-funded conditions, especially after the policy was implemented.

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*Table 4a: Conditions associated with utilization; Pharmacy Claims.*

| | Control Group | | | | | | Study Group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Index Event Pharmacy + Denied | | Index Event Pharmacy Claim | | Index Event Denied Claim | | Index Event Pharmacy + Denied | | Index Event Pharmacy Claim | | Index Event Denied Claim | |
| N= | 49 | % | 46 | % | 3 | % | 64 | % | 50 | % | 14 | % |
| **FDA Funded** | **38** | **77.6%** | **35** | **76.1%** | **3** | **100.0%** | **49** | **76.6%** | **38** | **76.0%** | **11** | **78.6%** |
| Rheumatoid Arthritis | 19 | 38.8% | 18 | 39.1% | 1 | 33.3% | 21 | 32.8% | 17 | 34.0% | 4 | 28.6% |
| Chronic Plaque Psoriasis | 15 | 30.6% | 15 | 32.6% | | 0.0% | 15 | 23.4% | 13 | 26.0% | 2 | 14.3% |
| Psoriatic Arthritis | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Ankylosing Spondylitis | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Crohn's Disease | 5 | 10.2% | 3 | 6.5% | 2 | 66.7% | 11 | 17.2% | 6 | 12.0% | 5 | 35.7% |
| Ulcerative Colitis | | 0.0% | | 0.0% | | 0.0% | 3 | 4.7% | 3 | 6.0% | | 0.0% |
| Multiple Sclerosis | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Oncology Indications | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Microscopic Polyangitis | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| **Off-Label Funded** | **0** | **0.0%** | **0** | **0.0%** | **0** | **0.0%** | **1** | **1.6%** | **1** | **2.0%** | **0** | **0.0%** |
| Wegener's granulomatosis | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Alzheimer's disease | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Behcet's disease | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Age-related macular degeneration | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Type 1 diabetes mellitus | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Gout | | 0.0% | | 0.0% | | 0.0% | 1 | 1.6% | 1 | 2.0% | | 0.0% |
| Systemic lupus erythematosus | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| Hepatitis C | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| **Unfunded Conditions** | **0** | **0.0%** | **0** | **0.0%** | **0** | **0.0%** | **0** | **0.0%** | **0** | **0.0%** | **0** | **0.0%** |
| Hidradenitis Suppurativa | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% | | 0.0% |
| **None of the Above** | **11** | 22.4% | **11** | **23.9%** | **0** | **0.0%** | **14** | **21.9%** | **11** | **22.0%** | **3** | **21.4%** |

*Table 4b: Conditions Associated with Utilization; Medical Claims.*

| | Control Group | | Study Group | |
|---|---|---|---|---|
| | Index Event Medical Claim | | Index Event Medical Claim | |
| N= | 128 | % | 65 | % |
| **FDA Funded** | **99** | **77.3%** | **46** | **70.8%** |
| Rheumatoid Arthritis | 47 | 36.7% | 21 | 32.3% |
| Chronic Plaque Psoriasis | 12 | 9.4% | 5 | 7.7% |
| Psoriatic Arthritis | | 0.0% | | 0.0% |
| Ankylosing Spondylitis | | 0.0% | | 0.0% |
| Crohn's Disease | 24 | 18.8% | 12 | 18.5% |
| Ulcerative Colitis | 9 | 7.0% | 8 | 12.3% |
| Multiple Sclerosis | 18 | 14.1% | 6 | 9.2% |
| Oncology Indications | | 0.0% | | 0.0% |
| Microscopic Polyangitis | 1 | 0.8% | | 0.0% |
| **Off-Label Funded** | **3** | **2.3%** | **0** | **0.0%** |
| Wegener's granulomatosis | | 0.0% | | 0.0% |
| Alzheimer's disease | | 0.0% | | 0.0% |
| Behcet's disease | | 0.0% | | 0.0% |
| Age-related macular degeneration | | 0.0% | | 0.0% |
| Type 1 diabetes mellitus | 1 | 0.8% | | 0.0% |
| Gout | 2 | 1.6% | | 0.0% |
| Systemic lupus erythematosus | | 0.0% | | 0.0% |
| Hepatitis C | 1 | 0.8% | | 0.0% |
| **Unfunded Conditions** | **0** | **0.0%** | **0** | **0.0%** |
| Hidradenitis Suppurativa | | 0.0% | | 0.0% |
| **None of the Above** | **26** | **20.3%** | **19** | **29.2%** |

Table 5 depicts the PA status for patients whose initial claim was denied both in the control and study group. Of the 14 patients in the study group with a denied claim, 6 requested a PA, which all were subsequently approved. Eight patients (57.1%) did not complete a PA request. Five study group patients were later seen in the ED or were hospitalized, 2 that had requested a PA and were approved, and 3 that did not request a PA. Profiles were reviewed for the 3 patients with no PA request and a 90-day hospitalization or ED visit. We were unable to determine why patients were hospitalized from claims data and were therefore unable to assess if a lack of therapy or delay of receiving biologic treatment lead to hospitalization or emergency care.

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Date: March 2016

*Table 5: PA status for Patients with Denied Pharmacy Claim.*

| | Control Group | | Study Group | |
|---|---|---|---|---|
| n= | *3* | 100.0% | 14 | 100.0% |
| **PA Requested** | **2** | **66.7%** | **6** | **42.9%** |
| *Approved* | *2* | 66.7% | *2* | *14.3%* |
| *Denied* | *0* | 0.0% | *0* | *0.0%* |
| **No PA Request** | **1** | **33.3%** | **8** | **57.1%** |

**Discussion:**

Overall, there was a decreased trend in total utilization of biologics since implementation of the PA. However, the decreased trend in index claims could be a result of numerous factors other than the PA itself, or the PA may deter prescribing of biologics for the treatment of inappropriate indications. The PA does not appear to further promote use of preferred biologic agents as preferred use only increased from 91.3% to 94.0% after implementation of the PA. Such high utilization of preferred products was not seen in the medical claims, however, for which there is no PA in place. However, the two preferred agents are not indicated for multiple sclerosis or cancer, which could account for lower preferred biologic use under medical claims. In addition, the preferred products are self-administered and would only be billed through the pharmacy claims. For more common indications like RA, Crohn's disease, or psoriasis, expanding the PA to the medical claims could promote a higher use of preferred products.

The majority of patients (76%) with a pharmacy claim for a biologic had a FDA-funded indication after the PA was implemented. The most common conditions were RA, Crohn's disease, and chronic plaque psoriasis. Of the remaining 24%, only one patient had an index pharmacy claim for an off-label funded condition while 22% of claims were for potentially oncology-related indications.

There was low use of a DMARD in the year prior to the index claim for a biologic agent. Based on pharmacy claims, the use of DMARD therapy was low (49%) before the PA was implemented and the rate did not change (48.4%) after the PA was implemented. PA criteria requests for most conditions that a trial with at least one first-line DMARD be tried before the patient is eligible for a biologic agent. Ideally, the PA would have increased prior use of a DMARD. However, the preferred agents are not subject to the PA so patients have access to a preferred biologic agent without requiring a trial of DMARD therapy. For medical claims, the rate of prior DMARD therapy was substantially lower at 18.2% which could be explained by different the associated conditions seen in this group (i.e., Crohn's disease, multiple sclerosis, and cancer) for which prior DMARD therapy is not standard of care. However, approximately a third of patients had a diagnosis of RA so there is opportunity to promote appropriate DMARD use on the medical claims.

After PA implementation, 5 of the 14 patients witha rejected PA were later hospitalized. Two of these patients submitted a PA request that was subsequently approved. Profile review of remaining 3 patients did not yield conclusive evidence that lack of biologic therapy was related to the hospitalization or ED visit.

Limitations to this evaluation include the small sample size and patients loss to follow-up. There are inherent limitations with claims data, including the inability to capture accurate diagnoses and treatments. There are also limited access to patient profiles that can result in a lack of clear associated indications, prior therapy, and causes of adverse events. In addition, there could be missing data from claims being paid for by another entity, such as veteran's affairs or co-insurance, or prior DMARD therapy could have occurred prior to the 100 day look back period. No PA is in place for preferred agents, which restricts the ability to enforce DMARD therapy before a biologic agent is utilized. Additionally, there are differences in first-line treatment for particular indications.

Author: Megan Herink, PharmD Date: March 2016

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**Appendix 1:** Prior Authorization Criteria

# Biologics for RA, Psoriasis, or Crohn's Disease

## Goal(s):

- Cover biologics according to OHP list guidelines.
- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products.

## Length of Authorization:

Up to 12 months

## Requires PA:

- All biologicals for indications other than:
  - Non-Hodgkin Lymphoma
  - Multiple Sclerosis

## Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Generic Name | Trade Name | Indication |
|---|---|---|
| Abatacept | Orencia | RA, juvenile RA, juvenile idiopathic arthritis |
| Adalimumab | Humira | RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease, plaque psoriasis, ulcerative colitis |
| Anakinra | Kineret | RA |
| Apremilast | Otezla | Psoriatic arthritis, plaque psoriasis |
| Certolizumab | Cimzia | RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis |
| Etanercept | Enbrel | RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis |
| Golimumab | Simponi | RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis |
| Infliximab* | Remicade | RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis |
| Natalizumab* | Tysabri | Crohn's disease, multiple sclerosis |
| Rituximab* | Rituxan | RA, CLL, Wegnener granulomatosis, Microscopic polyangiitis, non-Hodgkin lymphoma |
| Secukinumab | Cosentyx | Plaque psoriasis |
| Tocilizumab* | Actemra | RA, juvenile idiopathic arthritis |

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Date: March 2016

| | | |
|---|---|---|
| Tofacitinib | Xeljanz | RA |
| Ustekinumab | Stelara | Plaque psoriasis, psoriatic arthritis |
| Vedolizumab | Entyvio | Ulcerative colitis, Crohn's disease |

Abbreviations: CLL: chronic lymphocytic leukemia; RA: rheumatoid arthritis
*Must be billed via HCPC J-code and payment requires trial of preferred self-administered drug first.

| **Approval Criteria** | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code. | |
| 2. Is the diagnosis covered by OHP? | **Yes:** Go to #3 | **No:** Pass to RPH; Deny for medical appropriateness. |
| 3. Will the provider change to a preferred product? | **Yes:** Inform provider of preferred alternatives. | **No:** Go to #4 |
| 4. Is the prescription for rituximab for o Non-Hodgkin Lymphoma (ICD-10 C85.8x, C85.9x) or Chronic Lymphocytic Leukemia (ICD-10 C91.10, C91.11, C91.12)? | **Yes:** Approve for length of treatment. | **No:** Go to #5 |
| 5. Is the prescription for natalizumab for the treatment of multiple sclerosis (ICD-10 G35)? | **Yes:** Approve for length of treatment. | **No:** Go to #6 |
| 6. Is the diagnosis chronic plaque psoriasis (ICD-10: L400-404, L408-418, L448 ) and the product requested FDA approved for psoriasis (see table above)?<br><br>* Moderate/Severe psoriasis treatments are covered by the OHP | **Yes:** Go to #7 | **No**: Go to #9<br><br>Note: Seborrheic dermatitis (L2083, L210-219, L303), keroderma (L110, L83, L850-852, L870-872, L900-902, L906, L940, L943) or other hypertrophic and atrophic conditions of skin (L119, L572, L574, L664, L908-909, L918-919, L922, L985) are not covered by OHP. |

| Approval Criteria | | |
|---|---|---|
| 7. Is the Psoriasis Moderate/Severe? Defined as functional impairment and one or more of the following:<br>• At least 10% body surface area involved or with functional impairment?<br>• Hand, foot or mucous membrane involvement | **Yes:** Go to #8 | **No:** Pass to RPh; deny, not covered by the OHP. |
| 8. Has the patient tried and not had an adequate response to standard systemic therapies or has a contraindication to ALL of the following:<br>• High-potency topical corticosteroids: betamethasone dipropionate, clobetasol, fluocinonide<br>• At least one other topical agent: calcipotriene, tazarotene, anthralin<br>• At least one other systemic therapy: cyclosporine, methotrexate or acitretin | **Yes**: Approve for length of treatment; maximum 1 year. | **No:** Pass to RPh; deny for medical appropriateness. |
| 9. Is the diagnosis ankylosing spondylitis (ICD-10 M459) and the product requested is FDA approved for ankylosing spondylitis? | **Yes:** Approve treatment for up to 1 year. | **No:** Go to #10 |
| 10. Is the diagnosis rheumatoid arthritis (ICD-10 M069, M0500, M0530, M0560, M061, M0800, M083, M0840, M1200, M0510, M064) or psoriatic arthropathy (ICD-10 L4054, L4059) and the product requested FDA approved for rheumatoid arthritis (see table above)? | **Yes:** Go to #11 | **No:** Go to #14 |
| 11. Has the patient had a trial and inadequate response to methotrexate or other first line DMARDs (leflunomide, sulfasalazine, hydroxychloroquine) and a disease duration of ≥6 months?<br>**OR**<br>An intolerance or contraindication to oral DMARDs? | **Yes:** Go to #12 | No: Pass to RPh; deny for medical appropriateness. |

| Approval Criteria | | |
|---|---|---|
| 12. Is the request for tofacitinib? | **Yes:** Go to #13 | **No:** Approve treatment for up to 1 year. |
| 13. Has the patient had a trial and inadequate response or intolerance to 1 or more biologic agent (Humira, Enbrel, Cimzia, Simponi, Orencia)? | **Yes:** Approve treatment for up to 1 year. | **No:** Pass to RPh; deny for medical appropriateness. |
| 14. Is the diagnosis Crohn's disease (ICD-10 K5000, K5010, K5080, K5090) or ulcerative colitis (ICD-10 K5100, K5120, K5130, K5140, K5150, K5180, K5190) and the product requested FDA approved for the indication (see table above)? | **Yes:** Go to #15 | **No:** Pass to RPh; deny for medical appropriateness. |
| 15. Has the patient had a trial and inadequate response to conventional therapy including immunosuppressive therapy (mercaptopurine, azathioprine) and/or corticosteroid treatments?<br>**OR**<br>Has an intolerance or contraindication to conventional therapy? | **Yes:** Approve treatment for up to 1 year. | **No:** Pass to RPh; deny for medical appropriateness. |

*P&T/DUR Review:* *7/15; 9/14; 8/12*
*Implementation:* *10/15; 9/27/14; 2/21/13*

**Appendix 2: Codes identifying Biologics in fee-for-service or managed care pharmacy claims**:

| GSN | Brand | Generic | FormDesc | PDL |
|---|---|---|---|---|
| 061205 | HUMIRA | ADALIMUMAB | PEN IJ KIT | Y |
| 061205 | HUMIRA CROHN'S | ADALIMUMAB | PEN IJ KIT | Y |
| 061205 | HUMIRA PSORIASIS | ADALIMUMAB | PEN IJ KIT | Y |
| 051599 | HUMIRA | ADALIMUMAB | SYRINGEKIT | Y |
| 051599 | HUMIRA PEDIATRIC CROHN'S | ADALIMUMAB | SYRINGEKIT | Y |
| 063724 | HUMIRA | ADALIMUMAB | SYRINGEKIT | Y |
| 072952 | HUMIRA | ADALIMUMAB | SYRINGEKIT | Y |
| 061938 | ENBREL | ETANERCEPT | PEN INJCTR | Y |
| 058214 | ENBREL | ETANERCEPT | SYRINGE | Y |
| 062624 | ENBREL | ETANERCEPT | SYRINGE | Y |
| 040869 | ENBREL | ETANERCEPT | VIAL | Y |
| 067681 | ORENCIA | ABATACEPT | SYRINGE | N |
| 060226 | ORENCIA | ABATACEPT/MALTOSE | VIAL | N |
| 048899 | KINERET | ANAKINRA | SYRINGE | N |
| 072076 | OTEZLA | APREMILAST | TAB DS PK | N |
| 073370 | OTEZLA | APREMILAST | TAB DS PK | N |
| 072075 | OTEZLA | APREMILAST | TABLET | N |
| 063903 | CIMZIA | CERTOLIZUMAB PEGOL | KIT | N |
| 065189 | CIMZIA | CERTOLIZUMAB PEGOL | SYRINGEKIT | N |
| 065113 | SIMPONI | GOLIMUMAB | PEN INJCTR | N |
| 071262 | SIMPONI | GOLIMUMAB | PEN INJCTR | N |
| 065114 | SIMPONI | GOLIMUMAB | SYRINGE | N |
| 071017 | SIMPONI | GOLIMUMAB | SYRINGE | N |
| 071250 | SIMPONI ARIA | GOLIMUMAB | VIAL | N |
| 040650 | REMICADE | INFLIXIMAB | VIAL | N |
| 058384 | TYSABRI | NATALIZUMAB | VIAL | N |
| 036870 | RITUXAN | RITUXIMAB | VIAL | N |
| 073395 | COSENTYX PEN | SECUKINUMAB | PEN INJCTR | N |
| 073395 | COSENTYX PEN (2 PENS) | SECUKINUMAB | PEN INJCTR | N |
| 073394 | COSENTYX (2 SYRINGES) | SECUKINUMAB | SYRINGE | N |
| 073394 | COSENTYX SYRINGE | SECUKINUMAB | SYRINGE | N |
| 071590 | ACTEMRA | TOCILIZUMAB | SYRINGE | N |
| 065409 | ACTEMRA | TOCILIZUMAB | VIAL | N |
| 065410 | ACTEMRA | TOCILIZUMAB | VIAL | N |
| 065411 | ACTEMRA | TOCILIZUMAB | VIAL | N |
| 070233 | XELJANZ | TOFACITINIB CITRATE | TABLET | N |
| 065993 | STELARA | USTEKINUMAB | SYRINGE | N |
| 065994 | STELARA | USTEKINUMAB | SYRINGE | N |
| 072362 | ENTYVIO | VEDOLIZUMAB | VIAL | |

**Appendix 3: Codes identifying Biologics in fee-for-service or managed care professional claims**

| J Code | Brand | Generic | PDL |
|---|---|---|---|
| J0129, C9230 | Orencia™ | Abatacept | N |
| J0135 | Humira™ | Adalimumab | Y |
| | Kineret™ | Anakinra | N |
| | Otezla™ | Apremilast | N |
| J0717, J0718, C9249 | Cimzia™ | Certolizumab | N |
| J1438 | Enbrel™ | Etanercept | Y |
| J0602 | Simponi™ | Golimumab | N |
| J1745 | Remicade™ | Infliximab | N |
| J2323, C9126, Q4079 | Tysabri™ | Natalizumab | N |
| J9310 | Rituxan™ | Rituximab | N |
| | Cosentyx™ | Secukinumab | N |
| J3262, C9264 | Actemra™ | Tocilizumab | N |
| | Xeljanz™ | Tofacitinib | N |
| J3357, C9261 | Stelara™ | Ustekinumab | N |
| J3490, C9026 | Entyvio™ | Vedolizumab | N |

Appendix 4: Codes identifying DMARD drugs and other conventional therapy in fee-for-service or managed care pharmacy or professional claims

| HIC3 | Class | GSN | Brand | Generic | TextDrugStr | FormDesc | Route | PDL |
|---|---|---|---|---|---|---|---|---|
| V1B | Antineoplastics, Oral | 036872 | METHOTREXATE | METHOTREXATE SODIUM | 2.5 mg | TABLET | PO | |
| S2N | STC 42 - Antiarthritics | 071561 | OTREXUP | METHOTREXATE/PF | 10 mg/0.4 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 071562 | OTREXUP | METHOTREXATE/PF | 15 mg/0.4 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 071563 | OTREXUP | METHOTREXATE/PF | 20 mg/0.4 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 071564 | OTREXUP | METHOTREXATE/PF | 25 mg/0.4 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 071563 | RASUVO | METHOTREXATE/PF | 20 mg/0.4 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072577 | RASUVO | METHOTREXATE/PF | 7.5 mg/0.15 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072578 | RASUVO | METHOTREXATE/PF | 10 mg/0.2 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072579 | RASUVO | METHOTREXATE/PF | 12.5 mg/0.25 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072580 | RASUVO | METHOTREXATE/PF | 15 mg/0.3 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072581 | RASUVO | METHOTREXATE/PF | 17.5 mg/0.35 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072582 | RASUVO | METHOTREXATE/PF | 22.5 mg/0.45 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072583 | RASUVO | METHOTREXATE/PF | 25 mg/0.5 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072584 | RASUVO | METHOTREXATE/PF | 27.5 mg/0.55 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 072585 | RASUVO | METHOTREXATE/PF | 30 mg/0.6 mL | AUTO INJCT | SQ | |
| S2N | STC 42 - Antiarthritics | 045266 | RHEUMATREX | METHOTREXATE SODIUM | 2.5 mg | TAB DS PK | PO | |
| V1B | Antineoplastics, Oral | 035928 | TREXALL | METHOTREXATE SODIUM | 10 mg | TABLET | PO | |
| V1B | Antineoplastics, Oral | 036874 | TREXALL | METHOTREXATE SODIUM | 7.5 mg | TABLET | PO | |
| V1B | Antineoplastics, Oral | 047823 | TREXALL | METHOTREXATE SODIUM | 5 mg | TABLET | PO | |
| V1B | Antineoplastics, Oral | 047824 | TREXALL | METHOTREXATE SODIUM | 15 mg | TABLET | PO | |
| S2I | STC 42 - Antiarthritics | 040549 | ARAVA | LEFLUNOMIDE | 10 mg | TABLET | PO | |
| S2I | STC 42 - Antiarthritics | 040550 | ARAVA | LEFLUNOMIDE | 20 mg | TABLET | PO | |
| S2I | STC 42 - Antiarthritics | 040549 | LEFLUNOMIDE | LEFLUNOMIDE | 10 mg | TABLET | PO | |
| S2I | STC 42 - Antiarthritics | 040550 | LEFLUNOMIDE | LEFLUNOMIDE | 20 mg | TABLET | PO | |
| D6F | Inflammatory Bowel Disease | 009402 | AZULFIDINE | SULFASALAZINE | 500 mg | TABLET | PO | Y |
| D6F | Inflammatory Bowel Disease | 009403 | AZULFIDINE | SULFASALAZINE | 500 mg | TABLET DR | PO | Y |
| D6F | Inflammatory Bowel Disease | 009402 | SULFASALAZINE | SULFASALAZINE | 500 mg | TABLET | PO | Y |
| D6F | Inflammatory Bowel Disease | 009403 | SULFASALAZINE DR | SULFASALAZINE | 500 mg | TABLET DR | PO | Y |
| D6F | Inflammatory Bowel Disease | 009402 | SULFAZINE | SULFASALAZINE | 500 mg | TABLET | PO | Y |
| D6F | Inflammatory Bowel Disease | 009403 | SULFAZINE EC | SULFASALAZINE | 500 mg | TABLET DR | PO | Y |
| Z2E | Immunosuppressants | 011963 | CYCLOSPORINE | CYCLOSPORINE | 100 mg | CAPSULE | PO | Y |

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|---|---|---|---|---|---|---|---|---|
| Z2E | Immunosuppressants | 011964 | CYCLOSPORINE | CYCLOSPORINE | 25 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 023883 | CYCLOSPORINE | CYCLOSPORINE, MODIFIED | 100 mg/mL | SOLUTION | PO | Y |
| Z2E | Immunosuppressants | 023881 | CYCLOSPORINE MODIFIED | CYCLOSPORINE, MODIFIED | 100 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 023882 | CYCLOSPORINE MODIFIED | CYCLOSPORINE, MODIFIED | 25 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 023885 | CYCLOSPORINE MODIFIED | CYCLOSPORINE, MODIFIED | 50 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 023881 | GENGRAF | CYCLOSPORINE, MODIFIED | 100 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 023882 | GENGRAF | CYCLOSPORINE, MODIFIED | 25 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 023883 | GENGRAF | CYCLOSPORINE, MODIFIED | 100 mg/mL | SOLUTION | PO | Y |
| Z2E | Immunosuppressants | 023881 | NEORAL | CYCLOSPORINE, MODIFIED | 100 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 023882 | NEORAL | CYCLOSPORINE, MODIFIED | 25 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 023883 | NEORAL | CYCLOSPORINE, MODIFIED | 100 mg/mL | SOLUTION | PO | Y |
| Z2E | Immunosuppressants | 011684 | SANDIMMUNE | CYCLOSPORINE | 100 mg/mL | SOLUTION | PO | Y |
| Z2E | Immunosuppressants | 011963 | SANDIMMUNE | CYCLOSPORINE | 100 mg | CAPSULE | PO | Y |
| Z2E | Immunosuppressants | 011964 | SANDIMMUNE | CYCLOSPORINE | 25 mg | CAPSULE | PO | Y |
| W4A | STC 32 - Antimalarials | 009580 | HYDROXYCHLOROQUINE SULFATE | HYDROXYCHLOROQUINE SULFATE | 200 mg | TABLET | PO | |
| W4A | STC 32 - Antimalarials | 009580 | PLAQUENIL | HYDROXYCHLOROQUINE SULFATE | 200 mg | TABLET | PO | |
| W1C | Tetracyclines, Oral | 009226 | MINOCYCLINE HCL | MINOCYCLINE HCL | 100 mg | CAPSULE | PO | N |
| W1C | Tetracyclines, Oral | 009227 | MINOCYCLINE HCL | MINOCYCLINE HCL | 50 mg | CAPSULE | PO | N |
| W1C | Tetracyclines, Oral | 009230 | MINOCYCLINE HCL | MINOCYCLINE HCL | 100 mg | TABLET | PO | N |
| W1C | Tetracyclines, Oral | 009231 | MINOCYCLINE HCL | MINOCYCLINE HCL | 50 mg | TABLET | PO | N |
| W1C | Tetracyclines, Oral | 042778 | MINOCYCLINE HCL | MINOCYCLINE HCL | 75 mg | CAPSULE | PO | N |
| W1C | Tetracyclines, Oral | 052057 | MINOCYCLINE HCL | MINOCYCLINE HCL | 75 mg | TABLET | PO | N |
| W1C | Tetracyclines, Oral | 060730 | MINOCYCLINE HCL ER | MINOCYCLINE HCL | 45 mg | TAB ER 24H | PO | N |
| W1C | Tetracyclines, Oral | 060731 | MINOCYCLINE HCL ER | MINOCYCLINE HCL | 90 mg | TAB ER 24H | PO | N |
| W1C | Tetracyclines, Oral | 060732 | MINOCYCLINE HCL ER | MINOCYCLINE HCL | 135 mg | TAB ER 24H | PO | N |
| W1C | Tetracyclines, Oral | 065433 | SOLODYN | MINOCYCLINE HCL | 65 mg | TAB ER 24H | PO | N |
| W1C | Tetracyclines, Oral | 065434 | SOLODYN | MINOCYCLINE HCL | 115 mg | TAB ER 24H | PO | N |
| W1C | Tetracyclines, Oral | 066683 | SOLODYN | MINOCYCLINE HCL | 55 mg | TAB ER 24H | PO | N |
| W1C | Tetracyclines, Oral | 066684 | SOLODYN | MINOCYCLINE HCL | 80 mg | TAB ER 24H | PO | N |
| W1C | Tetracyclines, Oral | 066685 | SOLODYN | MINOCYCLINE HCL | 105 mg | TAB ER 24H | PO | N |
| Z2E | Immunosuppressants | 051793 | AZASAN | AZATHIOPRINE | 75 mg | TABLET | PO | N |
| Z2E | Immunosuppressants | 051794 | AZASAN | AZATHIOPRINE | 100 mg | TABLET | PO | N |
| Z2E | Immunosuppressants | 011682 | AZATHIOPRINE | AZATHIOPRINE | 50 mg | TABLET | PO | Y |
| Z2E | Immunosuppressants | 011682 | IMURAN | AZATHIOPRINE | 50 mg | TABLET | PO | Y |