Rheumatoid arthritis is among the most common and potentially debilitating forms of inflammatory arthropathy. Early diagnosis and intervention is critical to improving long-term outcomes and ensuring optimal prognoses.

PriorityHealth covers 630,000 lives across Michigan in commercial, self-funded, and government programs. The plan spends approximately $400 million annually on prescription drugs, with specialty medications—including biologics for the treatment of RA—comprising roughly 20% of that spend.

Since the approval of the first biologic therapy for rheumatoid arthritis in 1999, seven additional biologic agents have been approved specifically for treating RA; yet there remain unmet needs in managing this disease.
Many Moving Parts

In this issue, the first supplement for ManagedCare Oncology, we evaluate medical benefit insufibles outside of cancer care. You may be asking why we would do this. Our 2010 ICORE Healthcare Medical Injectables & Oncology Trend Report™ shows that about a quarter of drugs paid under the medical benefit are used to treat rheumatologic diseases. Also of interest is that infliximab (Remicade) is most commonly found to be the medical benefit drug with the highest total allowed amount per year - more than $11 million for every 1 million commercial lives. The management of rheumatologic disorders is more straightforward than cancer for sure; however, I believe that confusion exists. Here are some background thoughts that you may consider when developing your biologic response modifier (BRM) management strategy:

1. Efficacy. While few head-to-head comparisons exist, the Cochrane Report suggests that with the exception of anakinra (Kineret) all products are equally effective.

2. Cost. While a detailed discussion of the total cost of care is beyond the scope of this correspondence, each plan needs to evaluate the total cost of care. Importantly, drug administration costs are about $2,000 per year, and drug costs are approximately $5,000 greater annually for infused therapies; other costs, such as radiologic and laboratory studies, have generally been found to be similar across the available agents. Net costs must be calculated and are dependent on compliance and rebates.

3. Payment errors. Payment errors for office-infused drugs can occur at plans that do not have editing software in place. This virtually never occurs with self-administered drugs that are paid under the pharmacy benefit.

4. Variable dosing. Some critics of office-administered BRMs state that dose creep occurs over time; we have not found that to be true. In a three-year study of more than 2,037 BRM-utilizing members with 40,484 BRM prescriptions, little dose creep was detected. Interestingly, infliximab (Remicade) was found to have an average starting dose nearly twice the U.S. Food and Drug Administration label, as shown in Figure 2.

5. Process improvements. In our 2010 ICORE Healthcare Medical Injectables & Oncology Trend Report, we found that 91% of payors subjected office-administered BRM infusions paid under the medical benefit to prior authorization. While that statistic seems high, the process was most commonly limited to determining if the drug matched its indication. Few requests are denied based upon indication; while the real opportunity is to ask if a stepped-care protocol had been followed, if the initial starting dose and frequency are appropriate, and if the most cost-effective administration site is being chosen, this is seldom performed.

Today, the pipeline for both pharmacy and medical benefit BRMs is substantial. Think through the issues outlined above – now is the time to develop your management strategy to ensure the highest quality, most cost-efficient care for your members with rheumatologic disorders.

![Figure 1. Top Therapies that Use Provider-Administered Injectables](image1)

**Table 1. Top Therapies that Use Provider-Administered Injectables**

<table>
<thead>
<tr>
<th>THERAPEUTIC CLASS</th>
<th>ALLOWED PER 1M LIVES</th>
<th>% OF TOTAL SPEND*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV chemotherapy</td>
<td>$31,572,798</td>
<td>38%</td>
</tr>
<tr>
<td>Rheumatory</td>
<td>$19,021,848</td>
<td>23%</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor</td>
<td>$8,093,891</td>
<td>10%</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agent</td>
<td>$4,753,441</td>
<td>6%</td>
</tr>
<tr>
<td>Intravenous immune globulin</td>
<td>$2,205,164</td>
<td>3%</td>
</tr>
<tr>
<td>Oral chemotherapy</td>
<td>$3,971,891</td>
<td>5%</td>
</tr>
<tr>
<td>GRAND TOTAL</td>
<td>$69,619,033</td>
<td>84%</td>
</tr>
</tbody>
</table>

*Numbers sum less due to rounding errors

![Figure 2. Three-Year Dose Histogram Analysis of Infliximab (Remicade) at a 1.5 Million Life Commercial Payor](image2)

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**References**

3. ICORE Healthcare analysis of 1.5 million commercial members and 2,037 members with rheumatoid arthritis, 2009.

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**Editorial**

Kjel A. Johnson, PharmD
Publisher
ManagedCare Oncology

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**Focused On RA**

**SUPPLEMENT 1**
Facts & Figures

Facts & Figures provides snapshots of information key to managed care professionals. This installment features data regarding rheumatoid arthritis. We hope you find these facts and figures of value as you review your own health plan data.

Total Spend by Rheumatoid Arthritis Drug

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ALLOWED PER 1M LIVES</th>
<th>UNITS PER 1M LIVES</th>
<th>CLAIMS PER 1M LIVES</th>
<th>PATIENTS PER 1M LIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>$9,620,497.57</td>
<td>32,522</td>
<td>4,303</td>
<td>1,071</td>
</tr>
<tr>
<td>Humira</td>
<td>$5,279,196.82</td>
<td>7,798</td>
<td>2,457</td>
<td>592</td>
</tr>
<tr>
<td>Remicade</td>
<td>$2,971,113.37</td>
<td>36,569</td>
<td>1,038</td>
<td>333</td>
</tr>
<tr>
<td>Orenacna</td>
<td>$1,148,037.83</td>
<td>45,557</td>
<td>689</td>
<td>161</td>
</tr>
<tr>
<td>Rituxan</td>
<td>$822,014.95</td>
<td>6,922</td>
<td>166</td>
<td>68</td>
</tr>
<tr>
<td>Cimzia</td>
<td>$24,579.18</td>
<td>787</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>$6,903.84</td>
<td>3,063</td>
<td>857</td>
<td>219</td>
</tr>
<tr>
<td>Gold</td>
<td>$455.66</td>
<td>32</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td><strong>GRAND TOTAL</strong></td>
<td><strong>$19,872,799.23</strong></td>
<td><strong>134,050</strong></td>
<td><strong>9,538</strong></td>
<td><strong>2,455</strong></td>
</tr>
</tbody>
</table>

Source: ICORE Healthcare claims data representing 5 million commercial and Medicare lives, 14 months ending 8/31/10

Rheumatoid Arthritis Diagnosis – Drug Claims by Site of Service

(Allowed Claims per 1M Lives = $19,872,799)

Percentage of Drug Claims for RA Diagnosis Only

Source: ICORE Healthcare claims data representing 5 million commercial and Medicare lives, 14 months ending 8/31/10
Hematoid arthritis (RA) is among the most common and potentially debilitating forms of inflammatory arthropathy. The immune-mediated pathophysiology of this chronic and progressive disorder begins with inflammation of the synovium, manifesting in swelling, stiffness, warmth, redness, and pain in the joints. RA predominantly affects the extremities, with symmetrical inflammation in the joints of the hands and wrists being the most common presentation. The feet and ankles are also regularly affected, while involvement of larger joints – such as those in the knees and elbows – is less common. Beyond the immediate discomfort and limited range of motion brought on by synovial inflammation, RA can further lead to long-term joint damage that results in chronic pain, loss of function, and disability.

RA affects millions of Americans, with an incidence approximately 2.5 times greater in women than in men. Despite recent appreciation of an elderly onset component of the disease and misconceptions that all forms of arthritis are more common among older adults, the classic presentation of RA in females is postpartum in the years prior to menopause. In fact, among both sexes, the onset is typically during middle age, and RA often occurs in the 20s and 30s. The disease remains prevalent among the elderly, with an average age of 66.8 years, but the potential for RA to develop at any age makes it a burdensome condition in the private payer sector.

In addition to the significant pain and diminished physical function associated with RA, the disease can have a number of detrimental effects on patient health and well-being. The majority of RA sufferers report reduced quality of life,
clinically significant fatigue, and comorbid illness. Increased mortality is also a concern, as individuals with RA are more than twice as likely to die prematurely than an age- and sex-matched population of individuals without the disease. Furthermore, the aggressive course of RA often culminates in permanent joint damage and disability, with the initial structural damage frequently occurring within the first two years of the disease. As such, early diagnosis and intervention is critical to improving long-term outcomes and ensuring optimal prognoses.

**Diagnosis and Assessment**

Several disease-specific characteristics confound the diagnosis of RA and have led to the incorporation of multiple tools for identifying the disease and differentiating it from other joint conditions. No one single test can adequately diagnose RA by itself since symptoms can differ significantly from patient to patient and can be more severe in some individuals than in others. In addition, the full range of RA symptoms develops over time, and only a few symptoms may be present in the early stages. As a result of these interrelated yet varied characteristics of RA, a complete medical history and physical examination are necessary prior to laboratory tests and X-rays or other imaging studies for a comprehensive diagnosis.

After reviewing the patient’s medical history by looking at symptoms and the change of these symptoms over time, clinicians will generally evaluate the patient’s reflexes and overall health, including muscle strength. In addition, the affected joints are examined and the patient’s ability to bend, grasp, walk, and carry out activities of daily living are evaluated. If the physical examination indicates the presence of synovitis, a number of laboratory tests may be useful in confirming the diagnosis of RA. Among these tests are those for rheumatoid factor (RF), antibodies to cyclic citrullinated peptide (anti-CCP), complete blood count (CBC, i.e., to test for anemia), erythrocyte sedimentation rate, and C-reactive protein. Upon confirming the diagnosis, X-rays or other imaging studies may be employed to determine the extent of joint damage that has occurred through the inflammatory disease processes. While X-ray imaging is not as useful for diagnosing RA in the early stages, it may be used to rule out other causes of joint pain or to monitor the progression of the disease over time.

Similar to the varied roles of X-rays and imaging studies, many of the other aforementioned diagnostic tools may be employed to monitor disease progression and assess treatment effectiveness. By establishing a baseline of a patient’s disease characteristics with these tools at diagnosis, clinicians have a standard against which to measure the impact of the selected therapy and determine whether a change in dose or switch in medication is necessary to increase the likelihood of treatment success. In fact, this function of standard assessment tools is critical in treating RA since patients should ideally be on the appropriate intervention within the first two years of therapy to minimize permanent joint damage. The ultimate goal of RA treatment is remission, and that designation cannot be made without demonstrated elimination of disease activity by clinical, laboratory, and radiographic standards. As a result, clinicians employ RA assessment tools and clinical measures (e.g., health assessment questionnaire [HAQ], disease activity score [DAS], American College of Rheumatology [ACR] 20/50/70; Table 1) throughout the entire course of the disease.

**Table 1. Common Survey Tools for Assessing RA Disease Improvement**

<table>
<thead>
<tr>
<th>MEASURE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity score (DAS)</td>
<td>Statistically derived index consisting of number of tender joints, number of swollen joints, erythrocyte sedimentation rate, and global disease activity.</td>
</tr>
<tr>
<td>Health assessment questionnaire (HAQ)</td>
<td>Comprehensive outcome measure that assesses a hierarchy of patient outcomes in four domains: 1) disability, 2) discomfort/pain, 3) drug side effects (toxicity), and 4) dollar costs. Clinicians often employ only the disability and pain scales.</td>
</tr>
<tr>
<td>American College of Rheumatology 20/50/70</td>
<td>Measure requiring a patient to have either a 20%, 50%, or 70% reduction in the number of swollen and tender joints and a reduction of either 20%, 50%, or 70% in three of the following five parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and degree of disability in HAQ score.</td>
</tr>
</tbody>
</table>
Pharmacologic Treatment

The progressive and destructive nature of RA demands timely and aggressive therapy with disease-modifying antirheumatic drugs (DMARDs) and biologic response modifiers (BRMs) to slow disease development and permanent joint damage. While analgesics and anti-inflammatory drugs were once the primary mode of pharmacotherapy, clinicians have since recognized that these treatments merely suppress the symptoms associated with RA. Conversely, DMARDs and BRMs have been widely accepted as being necessary to inhibit or halt the underlying inflammatory processes of RA and prevent long-term joint damage. As a result, the traditional treatment approach – initiating with corticosteroids/ nonsteroidal anti-inflammatory drugs (NSAIDs) and progressing toward disease-modifying therapies – has been supplanted by a more proactive strategy employing DMARDs within three months of diagnosis (Figure 1).7,8

Among the traditional oral DMARDs, methotrexate is generally the initial agent selected for treatment, either alone or in combination with hydroxychloroquine. Other oral DMARDs, such as leflunomide, minocycline, and sulfasalazine, may also be prescribed in combination with methotrexate, which remains the cornerstone of first-line therapy. Since eliciting improvements in disease activity is critical for preventing disease progression and joint damage, the maximum effective DMARD dose may be achieved rapidly to save time and determine whether a therapy switch is necessary. In those patients who do not demonstrate an adequate response to DMARD therapy alone, the addition of a BRM is likely warranted.

ACR’s recommendations for the use of nonbiologic and biologic DMARDs in RA

Table 2. Measures of High Disease Activity and Features of Poor Prognosis in RA According to the American College of Rheumatology8

<table>
<thead>
<tr>
<th>MEASURES OF HIGH DISEASE ACTIVITY</th>
<th>THRESHOLD OF HIGH DISEASE ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity score in 28 joints</td>
<td>&gt; 5.1</td>
</tr>
<tr>
<td>Simplified disease activity index</td>
<td>&gt; 26</td>
</tr>
<tr>
<td>Clinical disease activity index</td>
<td>&gt; 22</td>
</tr>
<tr>
<td>RA disease activity index</td>
<td>&gt; 4.9</td>
</tr>
<tr>
<td>Patient Activity Scale/Patient Activity Scale II (PAS/PASI)</td>
<td>&gt; 5.3</td>
</tr>
<tr>
<td>Routine assessment patient index data</td>
<td>&gt; 12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FEATURES OF POOR PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional limitation (defined using standard measurement scales, such as health assessment questionnaire score or variations of this scale)</td>
</tr>
<tr>
<td>Extra-articular disease (e.g., presence of rheumatoid nodules, secondary Sjogren’s syndrome, RA vasculitis, Felty’s syndrome, and RA lung disease)</td>
</tr>
<tr>
<td>Rheumatoid factor positivity</td>
</tr>
<tr>
<td>Positivity for anticyclic citrullinated peptide antibodies</td>
</tr>
<tr>
<td>Bony erosions by radiography</td>
</tr>
</tbody>
</table>
also cite high levels of disease activity and features of poor prognosis as warranting a therapeutic switch to a BRM or even initiation of therapy on a BRM. Measures of high disease activity and features of poor prognosis are outlined in Table 2.

An antitumor necrosis factor α (anti-TNF) agent should be the initial BRM added to DMARD therapy for RA in clinically appropriate patients according to consensus recommendations (Figure 1). The currently approved anti-TNF agents include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab (Table 3). Of these, only infliximab is a professionally administered infused therapy, while the remaining anti-TNF agents are patient-administered injectables. In addition to this difference in mode of administration, the various anti-TNF therapies also differ in terms of dosing interval, which may play into patient convenience and preference of one agent over another. This is important because no single anti-TNF agent has demonstrated superior efficacy over the others for the treatment of RA (Table 4); therefore, choice of an initial agent is typically predicated on the discretion of the clinician or patient preference.

Table 3. Initial Dosing and Mode of Administration for FDA-Approved Anti-TNF RA Therapies

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>GENERIC NAME</th>
<th>MODE OF ADMINISTRATION</th>
<th>INITIAL DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>etanercept</td>
<td>SC, self-injected</td>
<td>50 mg q 1 wk</td>
</tr>
<tr>
<td>Remicade</td>
<td>infliximab</td>
<td>IV, provider-infused</td>
<td>3 mg/kg q 8 wk</td>
</tr>
<tr>
<td>Humira</td>
<td>adalimumab</td>
<td>SC, self-injected</td>
<td>40 mg q 2 wk</td>
</tr>
<tr>
<td>Cimzia</td>
<td>certolizumab</td>
<td>SC, self-injected</td>
<td>200 mg q 2 wk</td>
</tr>
<tr>
<td>Simponi</td>
<td>golumunab</td>
<td>SC, self-injected</td>
<td>50 mg q 4 wk</td>
</tr>
</tbody>
</table>

SC = subcutaneous injection; IV = intravenous infusion

Table 4. Comparable Efficacy of Approved Anti-TNF Agents in the Treatment of RA, as Defined by Performance in ACR Criteria in Clinical Trials

<table>
<thead>
<tr>
<th>ANTI-TNF AGENT</th>
<th>ACR 20</th>
<th>ACR 50</th>
<th>ACR 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
<td>59%-72%</td>
<td>29%-40%</td>
<td>13%-25%</td>
</tr>
<tr>
<td>infliximab</td>
<td>42%-66%</td>
<td>21%-50%</td>
<td>11%-37%</td>
</tr>
<tr>
<td>adalimumab</td>
<td>46%-63%</td>
<td>22%-42%</td>
<td>12%-23%</td>
</tr>
<tr>
<td>golimumab</td>
<td>34%-62%</td>
<td>16%-40%</td>
<td>10%-24%</td>
</tr>
<tr>
<td>certolizumab pegol</td>
<td>46%-59%</td>
<td>23%-37%</td>
<td>6%-21%</td>
</tr>
</tbody>
</table>

There are no strict guidelines for recommended duration of therapy with any BRM before a therapeutic switch is warranted, but three months appears to be adequate. This length of clinical response time should be applied rather than a specific number of doses administered since all the BRMs are dosed at different intervals, ranging from weekly to monthly. Among patients treated with agents offering dosing flexibility (e.g., abatacept, adalimumab, and infliximab), lowest approved dosing should be initiated, and then partial responders should have their doses escalated and their conditions reassessed prior to switching to other therapies. As mentioned previously, the clinical path of RA involves assessing and reassessing the elements that comprise remission (i.e., clinical, laboratory, and radiologic measures) to ensure that patients are either improving or are being efficiently switched to alternate therapies. Since time is of the essence in RA treatment, this clinical path has become less dependent on the patient’s impression of disease activity and more dependent on hard-and-fast markers such as evidence of bony erosions by radiography and erythrocyte sedimentation rate.

Future Directions in Managed Care
With a number of costly biologics in the
treatment armamentarium, RA represents a disease category frequently targeted for potential cost-saving interventions by payors. Specifically, there has been an increasing trend among managed care organizations for clinicians to prescribe the less costly, equally efficacious self-injected BRMs prior to initiating a trial of an infused agent, considering the comparable efficacy across the anti-TNF class. This typically takes the form of a step edit requiring treatment failure on at least one self-injected anti-TNF before allowing the use of an infused agent.

Even clinical guidelines from ACR acknowledge the impact of financial considerations on the course of treatment and recommend less costly modes of disease-modifying therapy. Although clinical considerations remain paramount in treatment selection, similarities in the effectiveness of the different anti-TNF agents necessitate clinicians’ awareness of patient out-of-pocket costs and the effect that they can have on patient preference of a particular therapy. In addition to increasing the likelihood of therapeutic adherence, prescribing with patient financial considerations in mind can engender patient trust in physicians.

Another patient-centered approach to assessing improvement in RA symptoms is also receiving attention as a means of enhancing the potential for treatment success. While the majority of clinicians are using one or more of the well-established survey tools to assess patient improvement in RA, most are missing an opportunity by not sharing these scores with their patients and explaining what the scores mean. Knowledge of the ACR 20/50/70, DAS, and HAQ measures can actually empower patients to take a more active role in their treatment and work toward improved outcomes with their physicians (Table 1). At present, these assessment tools are instead being used by physicians to meet payer requirements for dose increases, but the potential exists for expanded patient involvement and subsequent improvements in therapeutic adherence and lifestyle modification.

Optimal RA management strategies should encompass these patient-centered interventions, but early diagnosis and proactive evidence-based therapy remain absolutely indispensable for treatment success. Furthermore, with joint damage occurring early in the disease process, the ideally effective RA therapy for a particular patient must be identified in the most efficient manner possible. Still, with the high cost of biologics looming, this treatment selection process should be aggressive yet careful and deliberate in focus. Current utilization management directives, such as step edits, further allow plan stakeholders to facilitate the cost-effective use of BRMs, but a collaborative understanding must be reached between payors and providers in order to maximize efficiencies and ultimately improve outcomes in the management of RA.

References
Managing Costs and Optimizing Quality in the Treatment of Rheumatoid Arthritis: Considerations in the Era of Biologic Therapy

by Steve Marciniak, Director of Pharmacy, PriorityHealth

Arthritis and other rheumatic conditions, including rheumatoid arthritis (RA), result in an annual cost of nearly $128 billion in the United States. While indirect costs realized through lost productivity or absenteeism represent a portion of this total economic burden, the direct treatment costs associated with RA have risen significantly in the past decade with the advent of biologic therapies. Once a novel mode of therapy in managed care, these costly specialty products are being used much earlier and more frequently in the treatment of RA due to their demonstrated efficacy in slowing disease progression and limiting permanent joint damage. This has led to increased spending on RA therapies, impacting the pharmacy and medical budgets of payors due to the availability of therapies delivered via self-injection or provider-administered infusion. Not surprisingly, RA was the top therapeutic category contributing to pharmacy spending for specialty drugs in 2009, accounting for 26.8% of the total share (Figure 1).

RA represents a frustrating disease to manage from a pharmacy standpoint because there are so
few effective approaches to care other than pharmacologic treatment. As a result, the cost of care for the disease exists largely on the drug side and is characterized by issues related to the selected biologic’s formulation and mode of delivery: self-administered injectables or provider-infused agents. For self-injectables, the challenge lies in managing spend in the face of presumably unsustainable annual 10% cost increases by the manufacturers. Meanwhile, the primary cost-related challenge for infused RA therapies is managing the variable dose and dosing intervals associated with these clinician-administered drugs. While weight-based dosing and adaptable dosing intervals make infused agents, such as infliximab, a flexible treatment option for clinicians and patients, this variability adds a whole new layer of complexity to management on the payor side and increases the potential for inappropriate use.

In this manner, cost-related concerns associated with specialty biologic therapies for the treatment of RA are, at the same time, inextricably linked to quality-of-care issues.

The most visible barriers impeding the quality of care in RA exist on two fronts: 1) nonadherence on the part of patients and 2) inappropriate drug selection and dosing on the part of practitioners. In the face of these challenges with respect to the cost and quality of care in RA, payors are charged with the task of designing evidence-based management interventions that can help curb spending while driving appropriate use and sound clinical judgment on the part of clinicians.

**The PriorityHealth Experience**

PriorityHealth covers 630,000 lives across the state of Michigan in commercial, self-funded, and government programs. The plan spends approximately $400 million annually on prescription drugs, with specialty medications – including biologics for the treatment of RA – comprising roughly 20% of that spend. To characterize these RA drug expenditures further, plan stakeholders at PriorityHealth initiated an analysis of cost per unique member to obtain a realistic picture of spending on RA treatment. The resultant data clearly demonstrated a much higher cost associated with members on provider-infused therapies compared with self-injected therapies. A number of factors appeared to drive the higher spend tied to infused products, specifically drug cost, drug dose and frequency, and administration fees.

As a result of this analysis, in March 2009, PriorityHealth implemented a clinically sound algorithm for the management of RA. This algorithm follows a logical progression from oral disease-modifying antirheumatic drugs (DMARDs) to self-injectable tumor necrosis factor (TNF) inhibitors and finally to infused anti-TNF agents and other infused biologic response modifiers (BRMs). Self-injectables are subject to prior authorization (PA) and require a previous trial and failure of DMARDs. Likewise, infused products require a trial and failure of a self-injectable in order to be granted PA. Initial approvals for self-injectables are limited to three months,
with a requirement that clinical improvement be demonstrated before an additional 12-month authorization is granted. For provider-infused agents, the initial authorization applies for the induction phase, and authorization is again extended out to a year if positive clinical outcomes are demonstrated after induction therapy.

Aside from FDA-approved labeling and applicable data from the available literature, PriorityHealth relied on its internal clinical resources in developing its RA treatment algorithm and associated step-therapy criteria. This was done to gain unique insights from clinical practice and to ensure that the plan was not making any changes that would result in reduced quality of care due to resistance from network providers. Plan stakeholders met with area rheumatologists as the policies were developed. This process involved a discussion of whether the plan should take control of infliximab and other infused BRMs by routing these products through the specialty pharmacy, thereby eliminating buy-and-bill. After meeting with network providers, a compromise was reached in which the applicable providers could continue to infuse these products in their offices after a trial of a self-injected anti-TNF agent.

It was critical that PriorityHealth had its clinical rationale locked down before plan stakeholders took the recommendation to the Pharmacy and Therapeutics (P&T) committee. After P&T approval, the plan sought to effectively communicate the changes to all affected stakeholders, primarily the specialists who were prescribing and/or administering infused products. Further minimizing provider and member resistance, there are, of course, exceptions made to the step-therapy requirements for special cases. For those members who are physically unable to self-administer their therapy because of disability associated with their RA, infused agents are authorized without a prior trial of a self-injected product. In addition, like most plans, PriorityHealth restricts coverage for most drugs to their FDA-approved indication; however, the plan also features policies and procedures for approving off-label use in certain situations where there is sufficient peer-reviewed evidence to support the request. The goal here is not to put up hurdles for providers, but rather to facilitate judicial, evidence-based use. As a result, plan stakeholders strive to be reasonable in approving off-label requests when the appropriate supporting data exists.

Although this reasonable and evidence-based approach to the utilization management of RA therapies at PriorityHealth minimized provider resistance to the algorithm and step-therapy requirements, one regulatory issue arose in the Medicare segment. Due to local coverage determination rules, the plan was not permitted to limit access to clinician-infused therapies for Medicare beneficiaries.

Specialty Pharmacy Management of Nonadherence

The aforementioned algorithm and its associated step-therapy safeguards address concerns surrounding the appropriate use of RA therapies at PriorityHealth, while the plan’s specialty pharmacy program helps to manage issues associated with therapeutic adherence. Since costly biologics for the treatment of RA represent compulsory expenditures for payors, it is critical to ensure that members are adherent to therapy to minimize wasting of financial resources. The specialty pharmacy program employed by PriorityHealth provides this level of oversight to monitor and promote
adherence among those treated with injectable anti-TNF agents. Specifically, members self-injecting their RA therapies are captured and managed on a monthly basis through the program, while members receiving infused products are not as tightly managed.

The program, managed by Diplomat Specialty Pharmacy, features a monthly phone call from a pharmacy representative to ascertain how a member is doing on his or her self-injected therapy. A requisite part of this monthly call is an inquiry about financial factors, including whether the member is having any trouble meeting the copayments or coinsurance for the therapy. Members who cite difficulties meeting their out-of-pocket cost-sharing requirements—a key factor driving nonadherence to specialty drugs—are routed through a copayment-assistance program that the vendor also provides. Conversely, individuals receiving clinician-administered infused products do not receive such support services through the specialty pharmacy, which may contribute to adherence issues in these members. In addition to exclusion from the specialty pharmacy program, the variable dosing and dose intervals associated with infused RA therapies make it difficult to track measures such as adherence in members receiving clinician-administered biologics.

**Results and Future Directions**

Prior to implementation of the RA management interventions outlined previously, PriorityHealth established a baseline with which to compare interim results. The plan lowered RA drug costs significantly in two ways. First, the manufacturers of self-injectable products increased rebate levels in return for a preferred status over provider-infused agents. Second, as a result of the program, the percentage of members using infused therapies dropped, resulting in a greater share of lower-cost self-injectables in the RA sector. Specifically, the plan observed an approximate 5% reduction in the number of RA patients receiving the provider-administered anti-TNF agent infliximab (i.e., from 20% to 15% of members with RA). Tied to this reduction in the use of clinician-administered infused products, PriorityHealth’s per-member-per-month cost in the RA sector also decreased.

Although the number of members receiving clinician-administered RA therapies at PriorityHealth has decreased as a result of current interventions, the plan is continually seeking a better way to manage these infused products given their flexible dosing and dosing intervals. In addition, plan stakeholders continue to monitor the RA drug pipeline to ensure that PriorityHealth is positioned to effectively address new products as they come to market. Still, regardless of a new therapy being approved, the plan’s policies are reviewed and updated on an annual basis by the P&T committee to reflect changes on the therapeutic landscape and emerging clinical literature. New policies or changes to existing policies are communicated directly to providers utilizing the affected drugs as well as to the provider community at large. The plan also ensures that their customer service representatives, provider account representatives, and other touch points are updated so that the entire member and provider community remains informed.

Despite the cost and quality improvements yielded through PriorityHealth’s RA-targeted programs, plan stakeholders strive to avoid, and even remove, medical management directives, such as prior authorizations, whenever possible. Taking a comprehensive look, the PriorityHealth decision leaders analyze the plan’s return, approval/denial ratios, and overall volume to determine the value of their management policies. While high costs remain a key concern in the RA specialty drug sector, the overall guiding policy is that the plan should never implement a program that diminishes the quality of available care. PriorityHealth’s self-injectable first algorithm for RA fits these criteria. Prior to implementation, research showed that the plan was on clinically firm ground in the program’s fundamental design, and the results thus far have demonstrated that cost savings can be returned without sacrificing quality of care.

**References**


The approval of the first biologic therapy for rheumatoid arthritis (RA) in 1999 forever changed the landscape of RA therapy.

by Eric M. Ruderman, MD, Associate Professor of Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine

Since that time, seven additional biologic agents have been approved by the U.S. Food and Drug Administration (FDA) specifically for use in the treatment of RA, yet there remain unmet needs in the management of this disease. Current management guidelines call for the addition of disease-modifying antirheumatic drug (DMARD) therapy (usually methotrexate) at the time of diagnosis of RA and the addition of a second agent (usually a tumor necrosis factor [TNF] antagonist) in the event of inadequate response. With this approach, clinical trials have demonstrated an ability to achieve remission by standardized criteria in approximately 50% of patients. This leaves another 50% of patients with persistent disease, however, indicating a need for additional options.

Management of RA must address two therapeutic targets: improvement in clinical signs and symptoms and inhibition of structural damage, considered a surrogate for long-term functional impairment. Historically, persistence of objective inflammation has been closely tied to the progression of joint damage, but recent trials with TNF antagonists have suggested a disconnect between the two, with evidence for inhibition of radiographic progression despite ongoing clinical disease activity. Newer agents will need to demonstrate significant impact on both clinical
HORIZON
symptoms and radiographic progression in order to find a place in the therapeutic armamentarium.

Among biologic agents approved to date, the most common targets have been inflammatory cytokines, signaling proteins that drive both local and systemic inflammation. Five TNF antagonists are now approved for use in the U.S., along with an interleukin-1 receptor antagonist (anakinra) and a monoclonal antibody (tocilizumab) against the interleukin-6 (IL-6) receptor. Given the success of this approach, it is no surprise that several additional agents targeting other cytokine signaling pathways are in development.

ALD518, an antibody directed against IL-6 itself, rather than its receptor, has been studied in a phase 2 trial in 127 patients. When administered in combination with methotrexate, doses ranging from 80 mg to 320 mg given intravenously every eight weeks demonstrated response rates comparable to other effective biologic therapies in RA, with 46% of the high-dose group achieving low disease activity after just two doses. Measurements of health-related quality of life were improved as well, though no radiographic end points were measured in this trial. Interestingly, serum transaminase and cholesterol elevations, seen with tocilizumab and postulated to be related to the presence of IL-6 receptors on hepatocytes, were also seen with ALD518. Toxicity will be further characterized in a planned phase 3 trial, which will use subcutaneous rather than intravenous dosing. Several other companies have monoclonal antibodies to IL-6 in preclinical and early clinical development.

Another cytokine that has received a lot of attention in RA is IL-17, which is produced by TH17 lymphocytes and has effects on pathways in the disease that lead to inflammation, cartilage damage, and bone resorption. Two monoclonal antibodies against IL-17 have progressed into phase 2 clinical trials. LY2438821, in a small dose-ranging study in 77 patients, achieved a statistically significant reduction in the 28-joint count disease activity score (DAS-28) at 10 weeks for two of three dosing arms compared with placebo. Secukinumab, a second anti-IL-17 antibody, achieved significantly better DAS-28 responses than placebo over 16 weeks in a study of 237 patients, although the benefit was modest enough that its manufacturer has reportedly decided not to move forward in RA. A pilot study of secukinumab in ankylosing spondylitis, however, showed much more positive results, so this compound may have more promise in other indications.

The success in RA of rituximab, a B-lymphocyte-depleting monoclonal antibody directed against CD20, has led to an interest in other B-cell-directed therapies. Unfortunately, phase 3 trials of ocrelizumab, the fully human version of rituximab, were halted by the Data and Safety Monitoring Board because of increased serious infections; this compound will not move forward in RA. Trials of agents targeting B-cell survival factors, including LY2127399, an antibody against B-cell-activating factor (BAFF), and belimumab, the anti-B-lymphocyte stimulator antibody recently approved for treating systemic lupus erythematosus (SLE), are ongoing in RA. Phase 2 trials of atacicept, a fusion protein that inhibits both BAFF and APRIL, another B-cell survival protein, failed to meet their end points in both methotrexate and TNF antagonist inadequate responders. This compound is no longer moving forward in RA but is being further evaluated in SLE. SBI-087, a subcutaneously administered small molecule with a CD20-binding domain, is being studied in a phase 2 trial in RA.

Abatacept is a fusion protein composed of CTLA4 and the Fc portion of a human IgG1 that was approved for the treatment of RA in 2005. The currently available formulation is administered intravenously every four weeks, usually at a dose of 750 mg. A subcutaneous formulation of abatacept, given as a weekly 125 mg dose, was recently shown to be equivalent to intravenous dosing in a six-month trial in 1,457 patients. While not a new compound, this new formulation is likely to gain traction in the RA population where self-administered therapy is often preferred.
By far, however, the greatest excitement over the RA pipeline has been generated by the orally administered small molecules that have finally begun to show promise in this disease. Multiple previous trials of P38 and other MAP kinase inhibitors have failed, either because of lack of efficacy or level of toxicity, or both, and development of these agents has been halted. Several other kinase inhibitors, however, have reached late-stage clinical development.

Janus kinases (JAK) are a family of cytoplasmic tyrosine kinases involved in the signaling of several different cytokines, including IL-6. Phosphorylation of these kinases leads to downstream phosphorylation of STAT (signal transducer of active transcription) proteins and signal transduction into the cell nuclei. There are several different forms of JAK proteins, and the JAK inhibitors in clinical development have differences in their specificities.

The compound furthest along in the development pathway is tofacitinib. This compound was previously known as tasocitinib, the designation under which several clinical trials are published, but its generic name was recently changed at the request of the FDA to avoid confusion with another compound. Tofacitinib has been studied in two dose-ranging phase 2 trials in RA, one as monotherapy and one in combination with methotrexate. In the monotherapy trial, 384 RA patients with active disease despite DMARD therapy were randomly assigned to one of six treatment arms that included placebo or one of five doses of tofacitinib for 24 weeks. A seventh treatment arm received 40 mg adalimumab subcutaneously every other week as an active comparator. The three higher doses of tofacitinib (5 mg, 10 mg, or 15 mg BID) were statistically superior to placebo for the primary end point, an ACR20 response (20% improvement in disease activity), at 12 weeks, as well as for several other secondary end points of clinical response. Tofacitinib response was numerically superior to adalimumab; however, the study was not powered to show a difference between therapies, and the response to adalimumab was uncharacteristically low in this trial. A second dose-ranging study of 507 patients with an inadequate response to methotrexate therapy, in which tofacitinib was added to background methotrexate, confirmed 5 mg, 10 mg, and 15 mg BID as the most effective doses. Once-daily dosing with 20 mg was not effective in this trial.

Based on the data from the phase 2 trials, tofacitinib was moved into phase 3 at doses of 5 mg and 10 mg BID. The results of a phase 3 monotherapy trial were recently reported.
events related to this agent included more effective than placebo. Adverse events were similarly effective, and all were nonbiologic DMARDs; INCB028050, a phase 2 trial in 127 patients with an JAK1 and 2, is also in development. In trials with radiographic end points. With methotrexate is ongoing, as are combination with methotrexate may switched to active therapy at 12 weeks. Toxicity of tofacitinib has primarily consisted of modest elevations in transaminases, LDL, and HDL, with some patients developing mild decreases in neutrophil counts. The incidence of serious infection was not higher than placebo in the phase 3 trial, and no opportunistic infections were reported. Data from these trials, along with an open-label extension of the phase 2 trials, suggest that combination with methotrexate may not increase the efficacy of tofacitinib, but it may increase the risk of adverse events. A phase 3 combination trial with methotrexate is ongoing, as are trials with radiographic end points.

INCB028050, a second JAK inhibitor that preferentially inhibits JAK1 and 2, is also in development. In a phase 2 trial in 127 patients with an inadequate response to biologic or nonbiologic DMARDs, INCB028050 doses of 4 mg, 7 mg, or 10 mg daily were similarly effective, and all were more effective than placebo. Adverse events related to this agent included increases in HDL and LDL but not transaminases, and there was a small dose-dependent decrease in hemoglobin.

Fostamatinib, a small-molecule inhibitor of spleen tyrosine kinase (Syk), an important mediator of Fcγ receptor signaling, has also moved into late-stage development. Early phase 2 trials with fostamatinib demonstrated efficacy in methotrexate inadequate responders but not in biologic failures. In a larger phase 2 trial of 457 patients with an inadequate response to methotrexate, fostamatinib doses of 100 mg BID and 150 mg daily were both superior to placebo at six months. The most frequent side effect with this compound has been diarrhea. Increased upper respiratory infections, neutropenia, and mild elevations in transaminases were also seen in this trial, along with hypertension, requiring initiation or increases in antihypertensive medication in 18% and 23% of the 150 mg and 100 mg dose groups, respectively. As with tofacitinib, there is no data on structural progression yet available with fostamatinib.

BMS-582949, another interesting small molecule in early development in RA, is a P38 kinase inhibitor that impedes both P38 kinase activity and its activation. A pilot study has suggested that this agent may be more effective than previous P38 inhibitors, possibly because it is able to inhibit feedback P38 activation that can blunt response over time.

Finally, a number of companies have selective glucocorticoid receptor modulators in preclinical and early clinical development. There is great interest in these agents, which may provide a safer alternative to glucocorticoids by uncoupling their anti-inflammatory effects from the transactivation-mediated engagement of glucocorticoid response elements in DNA that leads to many of their toxic effects.

After years in which parenterally administered biologic compounds represented the cutting edge in rheumatoid arthritis therapy, researchers are anxiously awaiting the movement of oral small molecules from the pipeline into clinical practice. It remains to be seen whether these agents offer sufficient benefit in terms of efficacy and toxicity to supplant the current standard of care and whether patients will favor oral drugs that need to be taken once or twice daily over self-administered injections given weekly or less frequently. In the current economic environment, there is no doubt that price will enter this decision as well.

References
Help manage MANY THREATS:

Rheumatoid Arthritis.
Psoriatic Arthritis.
Ankylosing Spondylitis.

Please see Brief Summary of full Prescribing Information on last pages of this advertisement.

Indications¹

Moderate to severe rheumatoid arthritis: HUMIRA is indicated, alone or in combination with methotrexate or other non-biologic DMARDs, for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

Psoriatic arthritis: HUMIRA is indicated, alone or in combination with non-biologic DMARDs, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis.

Ankylosing spondylitis: HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Please see Brief Summary of full Prescribing Information on last pages of this advertisement.
40 mg every other week. Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.

Safety Considerations¹

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA. Patients treated with HUMIRA also may be at risk for other serious adverse reactions including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.


Please see Important Safety Information, including BOXED WARNING on Serious Infections and Malignancy, on the following page.
Important Safety Information

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB),** including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before HUMIRA use and during therapy. Treatment for latent TB should be initiated prior to HUMIRA use.

- **Invasive fungal infections,** including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.

- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with HUMIRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- **Do not start HUMIRA in patients with an active infection, including localized infections.**

- **Exercise caution in patients with chronic or recurrent infection or with underlying conditions which may predispose them to infection,** patients who have been exposed to TB, patients with a history of opportunistic infection, or patients who have resided or traveled in regions where TB or mycoses are endemic.

- **Patients who develop a new infection should undergo a prompt and complete diagnostic workup, and appropriate antimicrobial therapy should be initiated.**

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which HUMIRA is a member. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- **The risks and benefits of HUMIRA treatment should be considered prior to initiating or continuing therapy in a patient with known malignancy.**

- **More cases of malignancies were observed among HUMIRA-treated patients compared to control patients in clinical trials.**

- **Non-melanoma skin cancer (NMSC) has been reported during clinical trials for HUMIRA-treated patients. All patients should be examined for the presence of NMSC prior to and during treatment.**

- **In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.**

- **Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use.**

- **Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.**

HYPERSENSITIVITY

- **Anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration.**

- **If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.**

HEPATITIS B VIRUS REACTIVATION

- **Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.**

- **Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy.**

- **Exercise caution in patients who are carriers of HBV and monitor them during and after treatment with HUMIRA.**

- **Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation.**

- **Exercise caution when considering resumption of HUMIRA therapy after appropriate treatment for HBV.**

NEUROLOGIC REACTIONS

- **TNF blockers, including HUMIRA, have been associated in rare cases with new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis and Guillain-Barre syndrome.**

- **Exercise caution when considering HUMIRA for patients with these disorders.**

HEMATOLOGIC REACTIONS

- **Rare reports of pancytopenia including aplastic anemia have been reported with TNF blockers. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA.**

- **Consider stopping HUMIRA in patients with significant hematologic abnormalities.**

CONGESTIVE HEART FAILURE

- **Worsening or new onset congestive heart failure (CHF) may occur.**

- **Exercise caution in patients with CHF and monitor them carefully.**

AUTOIMMUNITY

- **Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome.**

- **Discontinue treatment if symptoms of a lupus-like syndrome develop.**

IMMUNIZATIONS

- **Patients on HUMIRA should not receive live vaccines.**

- **It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy.**

DRUG INTERACTIONS

- **Biologic products: Concurrent use of anakinra or abatacept with HUMIRA is not recommended, as the combination of anakinra or abatacept with other TNF blockers has been associated with an increased risk of serious infections. This risk has also been observed with rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker.**

ADVERSE REACTIONS

- **The most common adverse reactions in HUMIRA clinical trials (incidence >10%) were: infections (e.g. upper respiratory, sinusitis), injection site reactions, headache, and rash.**


Please see Brief Summary of full Prescribing Information on the following pages of this advertisement.

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WARNINGS: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death (see Warnings and Precautions). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

HUMIRA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- With or without prior treatment with HUMIRA in the following: including reactivation of latent TB
- Patients with TB have frequently presented with disseminated or extrapulmonary disease.
- During therapy with HUMIRA: prior study in patients with TB
- Cases of active TB have also been reported in patients receiving TNF blocking agents. A history of TB disease, prior positive TB skin test, or prior treatment for TB does not preclude the need for TB testing in patients receiving HUMIRA. Anti-TB prophylaxis may be necessary in patients with active TB. HUMIRA may be discontinued if a patient develops a serious infection or sepsis.

- Tuberculosis, bacterial, viral, and fungal infections are due to opportunistic pathogens. The risk of reactivation of latent TB infection prior to initiating therapy in patients with chronic or recurrent infections should be considered prior to initiating therapy in patients with chronic or recurrent infections.

Patients should be monitored for the development of signs and symptoms of infection during and after treatment with HUMIRA, including any worsening of symptoms of existing infections. Antigen or antibody testing for TB should be considered at baseline and periodically during therapy. Treatment for latent TB infection prior to initiating therapy. Tests for latent tuberculosis infection may also be false negative while on therapy with HUMIRA. HUMIRA should be discontinued if a patient develops active tuberculosis or is suspected to have active tuberculosis or may have had contact with a patient with active tuberculosis.

Malignancies in Patients and Young Adults

HUMIRA is indicated for reducing signs and symptoms of rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and TNF blockers including HUMIRA. Among opportunistic infections, tuberculosis, opportunistic pathogens have been reported in patients receiving TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker. These patients were at a higher risk for the occurrence of HIST is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing clinical improvement, and slowing the structural damage associated with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs). Systemic conditions.

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing clinical improvement, and slowing the structural damage associated with moderately to severely active juvenile idiopathic arthritis in pediatric patients 4 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing clinical improvement, and slowing the structural damage associated with psoriatic arthritis in adults. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms, inducing clinical improvement, and slowing the structural damage associated with ankylosing spondylitis in adults. HUMIRA can be used alone or in combination with methotrexate.

Crohn’s Disease

HUMIRA is indicated for reducing signs and symptoms, inducing clinical improvement, and slowing the structural damage associated with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms, and inducing clinical improvement in patients who also have lost response or are intolerant to infliximab.

Pneumocystis Pneumonia

The concomitant use of HUMIRA and methotrexate in the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a clinician experienced in phototherapy and Warnings and Precautions.

CONTRAINdications

None

WARNINGS AND PRECAUTIONS

(see Boxed Warning)

Serious infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens have been reported in patients receiving TNF blockers including HUMIRA. Among opportunistic infections, tuberculosis, opportunistic pathogens have been reported in patients receiving TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker. These patients were at a higher risk for the occurrence of HIST is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

Malignancies in Adults

In the controlled portions of 32 global HUMIRA clinical trials in adult patients with rheumatoid arthritis, no difference was detected in anti-pneumococcal polysaccharide vaccine response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the second dose response in patients treated with HUMIRA.

CONTRAINdications

None
The most common adverse reactions leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.2%).

Infections: In the controlled portions of the 32 global HUMIRA clinical trials in adult patients with RA, PS, AS, CD and PsD that included 22,009 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. In a subgroup of 9404 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.07 per 100 patient-years and the rate of positive PPD conversion was 0.06 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB.

Tuberculosis and Gastrointestinal Infections: In 45 controlled and uncontrolled clinical trials in RA, PA, AS, CD, and PsD that included 22,009 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. In a subgroup of 9404 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.07 per 100 patient-years and the rate of positive PPD conversion was 0.06 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB.

Other Adverse Reactions: The data described below reflect only the clinical trials experience obtained with adalimumab, not necessarily with HUMIRA, the combination of adalimumab and MTX.

The combination of adalimumab and MTX was generally well tolerated in rheumatoid arthritis patients and ankylosing spondylitis patients in controlled trials. The most common adverse reactions occurring in the pediatric population treated with HUMIRA were skin reactions and injection site reactions.

Table 1: Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

<table>
<thead>
<tr>
<th>Condition</th>
<th>HUMIRA 40 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=705)</td>
<td>(N=690)</td>
<td></td>
</tr>
<tr>
<td>Adverse Reaction (Preferred Term)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>7%</td>
</tr>
<tr>
<td>Laboratory Tests*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory test abnormal</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Rash</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Acute infection</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Injection site reaction**</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Back pain</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

In the controlled portions of the clinical trials in patients with Crohn’s disease treated with HUMIRA, the rates of injection site reactions and infusion reactions were 3% and 1%, respectively. Approximately 5% (58 of 1062) of adult rheumatoid arthritis patients treated with HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing in vitro. Patients treated with concomitant methotrexate had a lower rate of antibody development than patients on HUMIRA monotherapy (1% vs 12%). No apparent correlation of antibody development to adverse reactions was observed.

In patients with juvenile idiopathic arthritis who were on HUMIRA monotherapy and subsequently withdrawn from treatment, who were on HUMIRA monotherapy and subsequently withdrawn from treatment, the rate of antibody development was 3%. In patients with plaque psoriasis, the rate of antibody development in patients with concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis patients. In patients with ankylosing spondylitis, the rate was 7% compared to 1% in rheumatoid arthritis patients. In patients with juvenile idiopathic arthritis treated with HUMIRA and 40 mg and 40 mg on 14 days and 15, respectively, followed by 40 mg every other week in patients with Concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis patients. In patients with ankylosing spondylitis treated with 24 mg every other week in patients with Concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis patients.

Patient Counseling

Patients should be advised of the potential benefits and risks of HUMIRA. Physicians should instruct their patients to read the Medication Guide before starting HUMIRA therapy and to reread each time the prescription is renewed.

Infections: Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients the importance of contacting their doctor if they develop any symptoms of infection, including bacteremia, intravenous fungal infections, and reactivation of hepatit B virus infections.

Malignancies: Patients should be counseled about the risk of malignancies while receiving HUMIRA.

Allergic Reactions: Patients should be advised to seek immediate medical attention if they experience any of the following signs and symptoms of anaphylaxis: skin rash, itching, respiratory distress, difficulty breathing, swelling of the face, tongue, lips or larynx.

Other Medical Conditions: Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, pulmonary edema, serious infections and opportunistic infections, and TB that may require discontinuation of HUMIRA. If serious infections and opportunistic infections are present, physicians should discontinue HUMIRA and other immunomodulators when indicated. Physicians should not advise patients to remove certain medications without discussing the potential risks and benefits.

Pregnancy Registry:

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to report pregnancy outcomes to the Pregnancy Registry.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B – There are no adequate and well-controlled studies in pregnant women. Basing the decision to continue or discontinue therapy on the drug to the theory that potential benefits are worth the potential risk to the fetus. Several months of gestation is the period of organ development for the tubercle bacillus. Some cases of tuberculosis have been fatal for patients treated with HUMIRA who were exposed to the drug during pregnancy.

OTHER DISEASES

Other diseases that may require discontinuation of HUMIRA include tuberculosis, opportunistic infections, and serious infections.

Multimere, new or worsening infections (all sub-types including psoriasis and pyoderma gangrenosum).

Patient Counseling: Systemic vaccinations

Drug Interactions

Methotrexate: Although methotrexate (MTX) reduces the apparent absorption of HUMIRA, the data suggest that the need for dose adjustment of either HUMIRA or MTX.

Biologic Products: In clinical studies in patients with RA, an increased risk of serious infections has been associated with the combination of the TNF blockers with anakinra or abatacept, with no added benefit, therefore, use of HUMIRA with anakinra or abatacept is not recommended in patients with RA (see Warnings and Precautions). A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. These and insufficient information to provide recommendations regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PA, AC, Crohn’s Disease and plaque psoriasis.

Live Vaccines: Live vaccines should not be given concurrently with HUMIRA (see Warnings and Precautions).

NonCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or to evaluate fertility outcomes. In general, caution should be used when treating the elderly.

OVERDOSAGE

Overdosage: No experience have been conducted to administer clinical trials without evidence of dose-limiting effects. In cases of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and take emergency medical treatment immediately.

Abbott

Abbott
The Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act on Cancer Care Delivery (ACA), passed in March 2010, primarily affect specialty care, including treatment of rheumatoid arthritis (RA), through controlling spending via a series of demonstration projects and new entities to evaluate the value (reflected by cost and outcomes) of care. Currently, many payors, including the federal government through Medicare and Medicaid, cover and reimburse for services and technologies based on either the provision or the price of services. Payment is not based on metrics of quality or value.

There are a number of provisions in the bill that, either explicitly or indirectly, have the potential to significantly affect how specialty care is delivered and reimbursed. The Secretary of the Department of Health and Human Services (HHS) has a number of new authorities granted under the ACA related to altering or testing alternative coverage and payment policies provided by the Centers for Medicare & Medicaid Services (CMS). The main vehicles for change are:

- Center for Medicare and Medicaid Innovation (CMMI)
- Independent Medicare Review Board (IMRB)
- National pilots on payment bundling
- Accountable care organizations (ACOs)
- Patient-Centered Outcomes Research Institute (PCORI)

Center for Medicare and Medicaid Innovation

The purpose of establishing the CMMI within the CMS is to test innovative payment and service delivery models to reduce Medicare or Medicaid expenditures while maintaining or improving the quality of care. The CMS often prefers to test out new ideas or systems through demonstrations or pilot projects prior to expanding an idea to the whole CMS program. The CMMI is targeting 66 projects in 2011, although many think it will be difficult for the group to get more than 30 off the ground given that, despite its independence, it is still operating within the bureaucracy of the CMS. Some of
the projects being discussed are care-management focused, collapsing the traditional siloed approach of the agency. One offers a head-to-head look at different modes of radiation, imposing least costly alternative payment policies across modalities. Another pilots specialty ACOs outside of the traditional proposed model that focuses on primary care.

National Pilots on Payment Bundling
A potential project within the CMMI or the Office of Strategic Planning (formerly the Office of Research and Demonstrations) within the CMS is the bundled pricing concept, which is of interest to many payors (both commercial and public). The ACA includes opportunities to test payment bundles in both Medicare and Medicaid. Bundled payments (also known as “case rates,” “episode-based payments,” or “total treatment packages”) create a single payment for all services related to a treatment or condition, possibly spanning multiple providers in multiple settings. A five-year pilot program is established in the ACA in which care will be integrated during and after a hospitalization for an episode of care provided to a beneficiary to improve coordination, quality, and efficiency of the healthcare provided. The applicable services are designated as acute inpatient; physicians’ services in and outside of the acute care setting; outpatient hospital services, including the emergency department; postacute services; and other services deemed appropriate. The episode of care is defined by three days prior to admission, length of stay, and 30 days following discharge. The Secretary of HHS has the authority to determine episodes of care as appropriate and will develop payment methods and quality metrics for the program.2

A second bundling project will evaluate the use of bundled payments for Medicaid beneficiaries. The project will start on January 1, 2012, and end on December 31, 2016. It will be conducted in up to eight states, selected by the Secretary based on the potential to lower costs under the Medicaid program while improving care.3

While these sections address inpatient and...
postacute care and are not likely applicable to diseases typically treated with biologics, these pilots must be closely monitored by those with interests in biologics, especially cancer treatments. Bundled payments provide incentives to better coordinate care through alignment with evidence-based best practices and clinical quality standards. Bundles identify clinical variation, standardize costs of effective care, and provide for identification and stratification of high-risk patients. These payment models are also valuable for strategic business decision making through cost and resource analysis and evaluation of the return on investment for disease management programs.

There has recently been an influx in the interest related to bundled payments for cancer care, specifically led by UnitedHealth Group, America's largest private payor, which started an episode-based pilot for oncology in spring 2009. UnitedHealth's first goal is to shift an oncologist's income away from drug sales so that going forward, income would not be dependent on how many drugs are sold but rather on how well the oncologist took care of the patient. The second goal is to create an environment where cancer clinicians would learn from one another based on actual performance comparisons. If the CMS moves in this direction as well, the impact for cancer care would be dramatic.

Payors (commercial and public) are increasingly interested in moving away from an average sales price-based methodology to decrease oncologists' reimbursement based on administering drugs, and the bundling demonstration could be an opportunity for the CMS to explore this concept.

**Accountable Care Organizations**

ACOs are proposed to be partnerships between hospitals and physicians designed to coordinate and deliver efficient care and provide payment based on value and quality rather than volume and intensity of service. The formation of these groups is intended to reduce overutilization and inefficiency, which in turn should lower healthcare costs.

In the ACA, ACOs are defined as groups of providers who work together to manage and coordinate care for Medicare beneficiaries. A pilot reimbursement provision utilizing ACOs requires that no later than January 1, 2012, the Secretary will establish a shared-savings program that promotes accountability for a patient population, coordinates services under Medicare Parts A and B (the inpatient and physicians’ services components), and encourages investment in infrastructure and redesigned care processes for high-quality and efficient service delivery. Group practices, practice networks, partnerships between hospitals and physicians, and hospitals employing physicians may work together to coordinate care for Medicare beneficiaries through an ACO. ACOs must have a minimum of 5,000 Medicare patients and sufficient primary care physicians to care for them. They must also have a legal structure in place to receive and distribute shared-savings payments, an effective leadership structure and processes to promote evidence-based care, and a minimum three-year Medicare contract.

Payments will continue to be made to providers in an ACO under the original Medicare fee-for-service (FFS; compared to Medicare Advantage or Medicare management care) program in the same manner, except that a participating ACO is eligible to receive payment for shared savings if the ACO meets quality performance standards. The provider will receive payment if the estimated average per-capita Medicare expenditures under the ACO for FFS are at least the percentage specified below the applicable benchmark. The Secretary will determine the appropriate percentage to account for normal variation in expenditures as well as estimate a benchmark for each agreement period using the most recent available three years of per-beneficiary expenditures for Parts A and B assigned to the ACO. If it is determined that an ACO is avoiding patients at risk to enhance the likelihood of increasing costs, it will be sanctioned or possibly terminated from the program.

To take advantage of incentive payments, providers need to prepare their organizations to report quality and performance data as they are developed and approved by the HHS. This includes investments in electronic health
records for data capture of a variety of health outcomes and cost information that can be easily analyzed. It should be noted that not all the regulatory requirements for ACOs have been released; the CMS anticipates a rule sometime in the very near future.

There are conflicting views about ACOs and how impactful they will be in altering the delivery of care. While some feel that ACOs are merely the flavor of the day and managed care of the 2010s, others are highly concerned about ACOs. Although many ACO pilots and demonstrations will not be implemented immediately and may have minimal short-term (the next one to three years) impact, it is inevitable that the CMS will continue to place downward pressure on the cost of specialty disease treatments through reimbursement and delivery reforms that emphasize primary care.

**Patient-Centered Outcomes Research Institute**

The ACA establishes a new comparative effectiveness research (CER) body, the PCORI. This institute will be formed as a nonprofit corporation that is not an agency of the U.S. government to provide assistance in healthcare decision making through the advancement of the quality and relevance of evidence of conditions. The Board of Governors, consisting of the Director of the Agency for Healthcare Research and Quality (AHRQ) (or designee), the Director of the National Institutes of Health (or designee), and 19 members who have been appointed by the comptroller general, will lead the PCORI. CER is defined as research that evaluates and compares health outcomes and the clinical effectiveness, risks, and benefits of two or more medical treatments, services, and items.

Because CER has been controversial, stemming from a concern that it will lead to rationing of health services, a further provision instructs that the Secretary of HHS may only use evidence and findings to make a determination regarding coverage if such use is through an iterative and transparent process that includes public scrutiny and comment. The bill clearly states that the Secretary is not authorized to deny coverage of items solely because of CER findings or to use the findings to determine treatment coverage, reimbursement, or incentive programs for certain subpopulations of patients.

The research findings may, however, be used by the Secretary in coordination with other findings to make coverage and reimbursement policies and to change a beneficiary’s out-of-pocket cost, thereby strongly encouraging patients to choose treatments deemed to be of higher quality or lower cost. Ongoing research into the cost and effectiveness of biotechnology treatments has the potential to change the services and products provided to patients as well as coverage by health plans. The cost-sharing and coverage provisions are a significant departure from current Medicare policy; the CMS will now be able to alter coverage or make beneficiaries face greater out-of-pocket costs based on its review of effectiveness. The impact for specialty products is especially great since they are highly prevalent and costly to the CMS – there is significant potential for novel therapies to be denied in the absence of strong evidence.

The Republican takeover of the U.S. House of Representatives may curb or delay some parts of the Obama administration’s healthcare reform agenda, but whether those aspects of the ACA focused on how specialty care is delivered and reimbursed will be affected remains to be seen. Both Democrats and Republicans have supported efforts to curb cost and quell reimbursement as long as patient access and appropriate medical care are left unfettered. So much of this change in America’s healthcare fabric is new that both sides will endure watchful waiting rather than make a misstep so close to a presidential election. One maxim is certain, again, and will guide our thinking going forward as we continue to maximize clinical utility and value for our customers – the only constant is change.

**References**

With each publication, ManagedCare Specialty Drugs highlights a particular disease state. This issue focuses on rheumatoid arthritis (RA), a long-term autoimmune disease that leads to inflammation of the joints and surrounding tissues and can also affect other organs. RA usually affects joints on both sides of the body equally. Wrist, fingers, knees, feet, and ankles are the most commonly affected. The course and the severity of the illness can vary considerably.

The following highlights medications that could be utilized in the management of rheumatoid arthritis.

This section addresses such topics as:
- Associated ICD-9-CM codes
- Drugs that have been approved by the U.S. Food and Drug Administration
- Drugs that are compendia-listed for off-label use based on clinical studies that suggest beneficial use in some cases
- Reimbursement and coding information
- HCPCS/CPT® codes and code description
- Current code price (AWP-based pricing)
- Most recent Medicare allowable (ASP + 6%), if applicable
- Possible CPT® administration codes that can be utilized with each drug

## Associated ICD-9-CM Codes:

- **714** Rheumatoid arthritis and other inflammatory polyarthropathies
  - Excludes rheumatic fever (390)
- **714.0** Rheumatoid arthritis
  - Arthritis or polyarthritis: atrophic rheumatic (chronic)
  - Use additional code to identify manifestation as: myopathy (359.6); polyneuropathy (357.1)
  - Excludes juvenile rheumatoid arthritis NOS (714.30)
- **714.1** Felty’s syndrome
  - Rheumatoid arthritis with splenomegaly and leukopenia
- **714.2** Other rheumatoid arthritis with visceral or systemic involvement
  - Rheumatoid carditis
- **714.3** Juvenile chronic polyarthritis
  - **714.30** Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
  - Juvenile rheumatoid arthritis NOS
  - Still’s disease
  - **714.31** Polyarticular juvenile rheumatoid arthritis, acute
  - **714.32** Pauciarticular juvenile rheumatoid arthritis
  - **714.33** Monoarticular juvenile rheumatoid arthritis
FDA-Approved Medications Currently Available to Treat Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>GENERIC (BRAND) NAME</th>
<th>HCPSC Code – Code Description</th>
<th>Current Code Price (AWP-Based Pricing) Effective 4/1/11</th>
<th>Medicare Allowable (ASP + 6%) – Effective 4/1/11-6/30/11</th>
<th>CPT* Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>abatacept (Orencia)</td>
<td>J0129 – injection, abatacept, 10 mg</td>
<td>$26.04</td>
<td>$20.65</td>
<td>96365, 96413*</td>
</tr>
<tr>
<td>adalimumab (Humira)</td>
<td>J0135 – injection, adalimumab, 20 mg</td>
<td>$503.09</td>
<td>$401.74</td>
<td>96372, 96401*</td>
</tr>
<tr>
<td>anakinra (Kinern)</td>
<td>J3590 – unclassified biologics</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>96372</td>
</tr>
<tr>
<td>azathioprine (Imuran)</td>
<td>J7500 – azathioprine, oral, 50 mg</td>
<td>$1.31</td>
<td>$0.14</td>
<td>N/A</td>
</tr>
<tr>
<td>azathioprine (Imuran)</td>
<td>J7501 – azathioprine, parenteral, 100 mg</td>
<td>$162.00</td>
<td>$106.78</td>
<td>96365</td>
</tr>
<tr>
<td>betamethasone acetate/ betamethasone sodium phosphate (Celestone Soluspan)</td>
<td>J0702 – injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg</td>
<td>$8.00</td>
<td>$5.83</td>
<td>11900, 11901, 20600, 20605, 20610, 96372</td>
</tr>
<tr>
<td>certolizumab pegol (Cimzia)</td>
<td>J0718 – injection, certolizumab pegol, 1 mg</td>
<td>$4.79</td>
<td>$4.03</td>
<td>96372, 96401*</td>
</tr>
<tr>
<td>corticotropin (Acthar HP)</td>
<td>J0800 – injection, corticotropin, up to 40 units</td>
<td>$3,054.00</td>
<td>$2,441.28</td>
<td>96372</td>
</tr>
<tr>
<td>dexamethasone sodium phosphate (e.g., Decadron, Dekasol)</td>
<td>J1100 – injection, dexamethasone sodium phosphate, 1 mg</td>
<td>$0.15</td>
<td>$0.08</td>
<td>11900, 11901, 20600, 20605, 20610, 96372, 96374</td>
</tr>
<tr>
<td>dexamethasone (Decadron)</td>
<td>J8540 – dexamethasone, oral, 0.25 mg</td>
<td>$0.09</td>
<td>$0.38</td>
<td>96372</td>
</tr>
<tr>
<td>etanercept (Enbrel)</td>
<td>J1438 – injection, etanercept, 25 mg (Code may be used for Medicare when drug is administered under the direct supervision of a physician; not for use when drug is self-administered.)</td>
<td>$256.34</td>
<td>$206.91</td>
<td>96372</td>
</tr>
<tr>
<td>gold sodium thiomalate (Myochrysine)</td>
<td>J1600 – injection, gold sodium thiomalate, up to 50 mg</td>
<td>$17.50</td>
<td>$15.06</td>
<td>96372</td>
</tr>
<tr>
<td>hydrocortisone sodium succinate (Solu-Cortef)</td>
<td>J1720 – injection, hydrocortisone sodium succinate, up to 100 mg</td>
<td>$2.33</td>
<td>$3.76</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>infliximab (Remicade)</td>
<td>J1745 – injection, infliximab, 10 mg</td>
<td>$82.81</td>
<td>$60.04</td>
<td>96365, 96366, 96413, 96415</td>
</tr>
<tr>
<td>methotrexate (Trexall, Rheumatrex)</td>
<td>J8610 – methotrexate, oral, 2.5 mg</td>
<td>$3.61</td>
<td>$0.11</td>
<td>N/A</td>
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<tr>
<td>methotrexate</td>
<td>J9250 – methotrexate sodium, 5 mg</td>
<td>$0.30</td>
<td>$0.19</td>
<td>96372, 96374, 96401, 96409, 96450</td>
</tr>
<tr>
<td>methotrexate</td>
<td>J9260 – methotrexate sodium, 50 mg</td>
<td>$0.04</td>
<td>$0.02</td>
<td>N/A</td>
</tr>
<tr>
<td>methylprednisolone (Medrol)</td>
<td>J7509 – methylprednisolone, oral, 4 mg</td>
<td>$0.68</td>
<td>$0.07</td>
<td>N/A</td>
</tr>
<tr>
<td>methylprednisolone (Depo-Medrol)</td>
<td>J1020 – injection, methylprednisolone acetate, 20 mg</td>
<td>$3.78</td>
<td>$1.37</td>
<td>11900, 11901, 20600, 20605, 20610, 96372</td>
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<tr>
<td>methylprednisolone (Depo-Medrol)</td>
<td>J1030 – injection, methylprednisolone acetate, 40 mg</td>
<td>$5.22</td>
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<td>11900, 11901, 20600, 20605, 20610, 96372</td>
</tr>
<tr>
<td>methylprednisolone (Depo-Medrol)</td>
<td>J1040 – injection, methylprednisolone acetate, 80 mg</td>
<td>$9.52</td>
<td>$5.80</td>
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</tr>
<tr>
<td>methylprednisolone (Depo-Medrol)</td>
<td>J2920 – injection, methylprednisolone sodium succinate, up to 40 mg</td>
<td>$2.36</td>
<td>$1.92</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>methylprednisolone (Depo-Medrol)</td>
<td>J2930 – injection, methylprednisolone sodium succinate, up to 125 mg</td>
<td>$4.15</td>
<td>$2.67</td>
<td>96365, 96366, 96372, 96374</td>
</tr>
<tr>
<td>methylprednisolone (Solu-Medrol)</td>
<td>J7510 – prednisolone, oral, 5 mg</td>
<td>$0.59</td>
<td>$0.03</td>
<td>N/A</td>
</tr>
<tr>
<td>methylprednisolone (Solu-Medrol)</td>
<td>J7506 – prednisone, oral, 5 mg</td>
<td>$2.95</td>
<td>$1.91</td>
<td>96372, 96374, 96401, 96409, 96450</td>
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<tr>
<td>prednisolone (Preleve)</td>
<td>J9310 – injection, rituximab, 100 mg</td>
<td>$699.65</td>
<td>$610.69</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>tocolvumab (Actemra)</td>
<td>J3262 – injection, tocilizumab, 1 mg</td>
<td>$3.98</td>
<td>$3.47</td>
<td>96365, 96413*</td>
</tr>
<tr>
<td>triamcinolone hexacetonide (Aristospan)</td>
<td>J3303 – injection, triamcinolone hexacetonide, 5 mg</td>
<td>$3.54</td>
<td>$1.29</td>
<td>11900, 11901, 20600, 20605, 20610</td>
</tr>
</tbody>
</table>

*Medicare may allow payment for chemotherapy administration codes for some nonchemotherapeutic agents, including monoclonal antibodies and other biologic response modifiers. Check with your local carrier for guidance as to which drugs fall into this category.
Compendia-Listed Off-Label-Use Medications Currently Available to Treat Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>GENERIC (BRAND) NAME</th>
<th>HPCPCS Code – Code Description</th>
<th>Current Code Price (AWP-Based Pricing)</th>
<th>Medicare Allowable (ASP + 6%) – Effective 4/1/11</th>
<th>CPT® Administration Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alemtuzumab (Campath)</td>
<td>J9010 – injection, alemtuzumab, 10 mg</td>
<td>$706.00</td>
<td>$588.70</td>
<td>96413, 96415</td>
</tr>
<tr>
<td>argatroban</td>
<td>C9121 – injection, argatroban, 5 mg</td>
<td>$31.52</td>
<td>APC Rate* $18.89</td>
<td>96365, 96366</td>
</tr>
<tr>
<td>argatroban**</td>
<td>J3490** – unclassified drugs</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>96365, 96366</td>
</tr>
<tr>
<td>chlorambucil (Leukeran)</td>
<td>J9999** – prescription drug, oral, chemotherapeutic, not otherwise specified</td>
<td>NDC level pricing</td>
<td>NDC level pricing</td>
<td>N/A</td>
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<tr>
<td>chlorambucil (Leukeran)</td>
<td>S0172 – chlorambucil, oral, 2 mg</td>
<td>$3.86</td>
<td>S0172 – not payable by Medicare</td>
<td>N/A</td>
</tr>
<tr>
<td>cyclophosphamide (Cytoxan)</td>
<td>J8530 – cyclophosphamide, oral, 25 mg</td>
<td>$2.09</td>
<td>$0.84</td>
<td>N/A</td>
</tr>
<tr>
<td>cyclophosphamide (Cytoxan)</td>
<td>J9070 – cyclophosphamide, 100 mg</td>
<td>$16.66</td>
<td>$7.56</td>
<td>96409, 96413, 96415</td>
</tr>
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<td>cyclosporine (Sandimmune)</td>
<td>J7516 – cyclosporine, parenteral, 250 mg</td>
<td>$26.83</td>
<td>$22.44</td>
<td>96365, 96366</td>
</tr>
<tr>
<td>mycophenolate (CellCept)</td>
<td>J7517 – mycophenolate mofetil, oral, 250 mg</td>
<td>$3.97</td>
<td>$1.31</td>
<td>N/A</td>
</tr>
<tr>
<td>tacrolimus (Prograf)</td>
<td>J7507 – tacrolimus, oral, 1 mg</td>
<td>$4.46</td>
<td>$2.79</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* APC (ambulatory payment classification) rates are for hospital OPPS (Outpatient Prospective Payment System) use only.
** When billing a nonclassified medication using a CMS 1500 claim form, you must include both the HCPCS code (e.g., J3590 for Kineret) in Column 24D and the drug name, strength, and NDC (National Drug Code) in Box 19 to ensure appropriate reimbursement.

CPT® Administration Code Descriptions

<table>
<thead>
<tr>
<th>CPT® ADMINISTRATION CODE</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11900</td>
<td>Injection, intralesional: up to and including seven lesions</td>
</tr>
<tr>
<td>11901</td>
<td>Injection, intralesional: more than seven lesions</td>
</tr>
<tr>
<td>20600</td>
<td>Arthrocentesis, aspiration and/or injection; small joint or bursa (e.g., fingers, toes)</td>
</tr>
<tr>
<td>20605</td>
<td>Arthrocentesis, aspiration and/or injection; intermediate joint or bursa (e.g., temporomandibular, acromioclavicular, wrist, elbow, ankle, olecranon bursa)</td>
</tr>
<tr>
<td>20610</td>
<td>Arthrocentesis, aspiration and/or injection; major joint or bursa (e.g., shoulder, hip, knee joint, subacromial bursa)</td>
</tr>
<tr>
<td>96401</td>
<td>Chemotherapy administration, subcutaneous or intramuscular; nonhormonal antineoplastic</td>
</tr>
<tr>
<td>96409</td>
<td>Chemotherapy administration; intravenous, push technique, single or initial substance/drug</td>
</tr>
<tr>
<td>96413</td>
<td>Chemotherapy administration, intravenous infusion technique; up to one hour, single or initial substance/drug</td>
</tr>
<tr>
<td>96415</td>
<td>Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure.) (Use 96415 in conjunction with 96413.)</td>
</tr>
<tr>
<td>96450</td>
<td>Chemotherapy administration, into CNS (e.g., intrathecal), requiring and including spinal puncture</td>
</tr>
<tr>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to one hour</td>
</tr>
<tr>
<td>96366</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure.) (Use 96366 in conjunction with 96365, 96367.)</td>
</tr>
<tr>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
<tr>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
</tr>
</tbody>
</table>

References

- FDA-approved indication (product-prescribing information).
- Compendia references available upon request.
- U.S. National Library of Medicine, National Institutes of Health.

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