AGENDA

State and Public School Life and Health Insurance Board
Drug Utilization and Evaluation Committee

December 14, 2015

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

I.	*Call to Order*	*Dr. Hank Simmons, Chairman*
II.	*Approval of October 26, 2015 Minutes*	*Dr. Hank Simmons, Chairman*
III.	*Targeted Immune Modulators*	*Dr. Rachael McCaleb, UAMS*
IV.	*EBD Report*	*Dr. Geri Bemberg, UAMS*

Upcoming Meetings

February 1, 2016

NOTE: All material for this meeting will be available by electronic means only asepse-board@dfa.arkansas.gov

Notice: Silence your cell phones. Keep your personal conversations to a minimum. Observe restrictions designating areas as "Members and Staff only"

State and Public School Life and Health Insurance Board
Clinical and Fiscal Drug Utilization and Evaluation Committee
Minutes
December 14, 2015

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday December 14, 2015 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

Voting Members present:
Dr. Scott Pace
Dr. Kat Neill – Vice-Chairman
Dr. Melodee Harris - Telephone
Larry Dickerson
Dr. Hank Simmons Chairman
Dr. Appathurai Balamurugan (Proxy)
Dr. William Golden
Dr. John Kirtley

Non-Voting Members present:
Dr. Jill Johnson
Connie Bennett
Dr. Geri Bemberg

Members absent:
Dr. Gary Wheeler – Ark Dept of Health

Lori Eden, Deputy Executive Director, Employee Benefits Division

OTHERS PRESENT
David Keisner, Jill Johnson, Rachel McCaleb, UAMS College of Pharmacy; Sherry Bryant, Ethel Whittaker, Janna Keathley, Shay Burleson, EBD; Marc Watts, ASEA; Takisha Sanders, Jessica Akins, Health Advantage; Ronda Walthall, Wayne Whitley, AHTD; Arlene Chan-Mouton, ACHI; Jon McGuire, GSK; Bridgett Johnson, Pfizer; Jim Chapman, Sean Teague, Merck; Connie Bennett, Optum RX; Treg Long, American Cancer Society; Karyn Langley, Qualchoice

CALL TO ORDER
Meeting was called to order by Dr. Hank Simmons, Chairman.

APPROVAL OF MINUTES
The request was made by Dr. Simmons to approve the October 26, 2015 minutes. Dickerson made the motion to approve. Dr. Neill seconded. All were in favor.

Minutes Approved.

TARGET IMMUNE MODULATORS: *by Dr. Rachael McCaleb, UAMS*

Targeted immune modulators (TIMs), also referred to as biologics, form a class of drugs for diseases with inappropriate immune response and chronic inflammation. These agents are used to treat diseases including; rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis psoriatic arthritis, inflammatory bowel diseases, and plaque psoriasis. These agenst selectively block the inflammatory and immune cascades.

The following table outlines currently available TIMs in the United States including route of administration, mechanism of action, and FDA approved (labeled) indication.

Drug	Route	MOA	RA	JIA	AS	PsA	Crohn's	UC	PP	Other
Abatacept **Orencia**	IV then SC		■	■						
Adalimumab **Humira**	SC		■	■	■	■	■	■	■	
Anakinra **Kineret**	SC		■							
Certolizumab **Cimzia**	SC		■		■	■	■			
Etanercept **Enbrel**	SC		■	■	■	■			■	
Golimumab **Simponi**	IV and SC		■		■	■		■		
Inflizimab **Remicade**	IV		■		■	■	■	■	■	
Natalizumab **Tysabri**	IV						■			
Vedolizumab **Entyvio**	IV						■	■		
Rituzimab **Rituxan**	IV		■							
Tocilizumab **Actemra**	IV		■	■						
Tofacitinib **Xeljanz**	PO		■							
Ustekinumab **Stelara**	SC					■			■	
Secukinumab **Cosentyx**	SC								■	

Abbreviations: AS, ankylosing spondylitis; IL, interleukin; IV, intravenous; JIA, juvenile arthritis; JAK, Janus kinase; MS, multiple sclerosis; NOMID, neonatal-onset multisystem inflammatory disease; PC, plaque psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC, subcutaneous; UC, ulcerative colitis; TNF, tumor necrosis factor
*= For moderate to severe disease in patients who have had an inadequate response with. Lost response to, or were intolerant to inhibitors of TNF infibitors corticosteroids

■ = FDA approved indication

PROPOSAL FOR CONTRACTING WIT DRUG MANUFACTURERS:

As outlined in the newly awarded PBM contract, EBRx will be starting the process of rebate contracting. With Targeted Immune Modulaters costing the plan over $3.5 million per quarter on the pharmacy side alone, this category was the DUEC's 1st choice for contract rebates on preferred drugs, but for themember as well through reduced copays on the same preferred medications.

Currently all TIMs medications are covered at Tier 4, with a $100 copay. The DUEC recommends that EBRx contract for at least 2 TIMS as preferred agents, while allowing for the other TIMs to remain on the formulary as non-preferred. Preferred agents will be placed at Tier s and have the Tier 2 copay of $40. Non-preperred agents will remain in their current tier placement, Tier 4, with a $100 copayment. NO current utilizers will be REQUIRED to switch their current drug regimen. However, in the event they choose to try a preferred agent in order to save themselves money in the form of copays, the plan will allow them to receive the medication for 4 months at a $0 copay. After 4 calendar months from the date of the first fill, the member will pay the Tier 2 copay of $40, a savings of $60 per month from the current tier placement. Should the member choose to stay with their current drug regimen, they will continue to pay their normal copay of $100 without penalty. The member will have 6 months from the time the rebate starts to take advantage of the copay waiver. No copay vaivers or reduced copays will be allowed for non-preferred agents, and waivers on preferred agents will only be approved for members switching from a nonpreferred agent. New TIMs utilizers will begin treatment on a preferred agent, and will be required to try a preferred agent(s) prior to gaining access to a non-preferred agent.

Prior authorization criteria will not be allowed to be a negotiating tool in the rebate contracting process, and will remain as it currently stands. The committee also recommends price protectin for the life of the contract, and that contracts be obtained that cover more than one (1) year.

In Summary:

- Include at least 2 preferred agents
    - Preferred agents will be moved to Tier 2, with a $40 copay.
    - Non-preferred agents will remain at Tier 4, with a $100 copay.
    - Members choosing to switch from a Tier 4 non-preferred agent to a Tier 2 preferred agent, will be allowed to receive the preferred drug at a $0 copay for 4 calendar months starting the date of the 1st fill. After 4 months, the member will pay the Tier 2 copay, $40.
    - Members wishing to take advantage of the copay waiver will have 6 months from the start date of the rebate to do so.
- No members will be required to switch their current drug regimen.
- No copay waivers will be allowed for non-preferred drugs.
- Prior authorization criteria will continue to all TIMs, and is not negotiable in the contracting process.
- Require price protection for the duration of the contract.

After detail discussion Dr. Golden recommended to move forward with a more detail report. Dr. Golden has concerns the current report could be misinterpreted.

Dr. Kirtley motioned to proceed with the development of the process. Dr. Golden seconded.

Discussion: Dr. Kirtley discussed proceeding with the development of the process which will allow

flexibility on input and how considerations need to clarified. Dr. Golden has concerns regarding the age limits approved by the FDA and the bidding process. Dr. Thompson reports the Board will have concerns with the cost effectiveness of the plan. Dr. McCaleb reports age limits will be removed.

Dr. Simmons reads the motion as follows: Motioned by Dr. Kirtley and seconded by Dr. Golden. The committee authorizes the group to go forward with preparing a more detailed proposal for submission to the Board that incorporates science and contractual language in seeking rebates. All were in favor.

Motion approved.

EBD REPORT*: by Dr. Geri Bemberg, UAMS*

Dr. Bemberg asked the committee for recommendations on the next category to be reviewed. The committee asked that insulins be reviewed. Also, the committee requested a report on the top drugs, drug categories, and disease states at the next meeting.

Meeting Adjourned

Targeted Immune Modulators (TIMs)

Rachael McCaleb, PharmD

December 14, 2015

Background:[1]

Targeted immune modulators (TIMs), also referred to as biologics, form a class of drugs for diseases with inappropriate immune response and chronic inflammation. These agents are used to treat diseases including; rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel diseases, and plaque psoriasis. These agents selectively block the inflammatory and immune cascades.

The following table summarizes currently available TIMs in the United States including route of administration, mechanism of action, and FDA approved (labeled) indication.

Drug	Route	MOA	RA	JIA	AS	PsA	Crohn's	UC	PP	Other
Abatacept[2] **Orencia®**	IV then SC	CD80/86-CD28 T-cell co stimulator		≥6y/o						
Adalimumab[3] **Humira®**	SC	TNF Inhibitor		≥4y/o			≥6y/o			
Anakinra[4] **Kineret®**	SC	IL-1 antagonist								NOMID
Certolizumab pegol[5] **Cimzia®**	SC	TNF Inhibitor								
Etanercept[6] **Enbrel®**	SC	TNF Inhibitor		≥2y/o						
Golimumab[7] **Simponi®**	IV and SC	TNF Inhibitor								
Infliximab[8] **Remicade®**	IV	TNF Inhibitor					≥6y/o			
Natalizumab[9] **Tysabri®**	IV	Anti-alpha-4 integrin subunit								MS
Vedolizumab[10] **Entyvio®**	IV	Anti-alpha-4-beta-7 integrin subunit					*	*		
Rituximab[11] **Rituxan®**	IV	Anti-CD 20a								
Tocilizumab[12] **Actemra®**	IV	IL-6 receptor inhibitor		≥2y/o						
Tofacitinib[13] **Xeljanz®**	PO	JAK inhibitor								
Ustekinumab[14] **Stelara®**	SC	IL-12/23 p40 inhibitor								
Secukinumab[15] **Cosentyx®**	SC	IL-17A receptor antagonist								

Abbreviations: AS, ankylosing spondylitis; IL, interleukin; IV, intravenous; JIA, juvenile arthritis; JAK, Janus kinase; MS, multiple sclerosis; NOMID, neonatal-onset multisystem inflammatory disease; PC, plaque psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC, subcutaneous; UC, ulcerative colitis; TNF, tumor necrosis factor

* = For moderate to severe disease in patients who have had an inadequate response with, lost response to, or were intolerant to inhibitors of TNF inhibitors or corticosteroids[10]

= FDA approved indication

Targeted Immune Modulators (TIMs)

Rachael McCaleb, PharmD

December 14, 2015

Evidence:

*Efficacy***:**

- For the treatment of rheumatoid arthritis (RA), there is low strength evidence that abatacept is more effective than infliximab in patients with an inadequate response to methotrexate a 1 year, although infliximab was administered at a fixed dose.[16]
- For the treatment of RA, there is low strength evidence that there is no difference between adalimumab and etanercept and that adalimumab and etanercept are more efficacious than infliximab.[17]
- For the treatment of RA, there is low strength evidence that abatacept was non-inferior to adalimumab in patients with an inadequate response to methotrexate.[18-19]
- For the treatment of RA, there is low strength evidence that tocilizumab is more effective than adalimumab in patients unable to tolerate methotrexate, although the dose of tocilizumab dose used was higher than Food and Drug Administration (FDA) approved.[20]
- For the treatment of RA, there is low strength evidence that there is no difference between tocilizumab, adalimumab, and etanercept[17] and tocilizumab, adalimumab, and abatcept[21].
- For the treatment of RA, there is low strength evidence that there is no difference between adalimumab and tofacitinib at 6 months in patients with an inadequate response to methotrexate.[22]
    - Although, at 12 weeks tofacitinib had a larger response than adalimumab.[22]
- For the treatment of RA, there is low strength evidence that combination therapies (etanercept and anakinra, etanercept and abatacept, and rituximab and adalimumab or etanercept) had limited added benefit but caused significantly higher adverse events.[23-25]
- There is insufficient evidence on the comparative effectiveness of TIMs for treatment of psoriatic arthritis and Crohn's disease.
- There is no evidence on the comparative effectiveness of TIMs for treatment of juvenile idiopathic arthritis (JIA), ankylosing spondylitis, and ulcerative colitis.
    - However, the minimum age requirement treatment of JIA differs for the agents; abatacept (≥6 years old), adalimumab (≥4 years old), etanercept (≥2 years old), and tocilizumab (≥2 years old).[2,3,6,12]
- Adalimumab and infliximab are approved for the treatment of ulcerative colitis in pediatric patients (≥6 years old).[3,8]
- There is low quality evidence that ustekinumab produced a significantly better response than etanercept in patients with moderate to severe plaque psoriasis (67.5-73.8% vs 56.8%; P<0.001).[26]
- Secukinumab was superior to ustekinumab in plaque psoriasis with respect of 90% or more improvement from baseline Psoriasis Area and Severity Index score (PASI90) at 16 weeks (79% vs 57.6%; P<0.0001).[27]
- Infliximab was shown to have the highest estimated mean probability of response or relative risk for the treatment of plaque psoriasis in a network meta-analysis compared to ustekinumab, adalimumab, etanercept, efalizumab.[28]

Targeted Immune Modulators (TIMs)

Rachael McCaleb, PharmD

December 14, 2015

Safety:[1]

- There is moderate strength evidence that infliximab was an increased risk of therapy discontinuation due to adverse effects than adalimumab and etanercept.
    - There is low strength evidence that infliximab has more serious adverse events than abatacept.
- Injection site reaction were more frequent with adalimumab and infliximab compared to abatacept (low strength) and etanercept compared to ustekinumab (low strength).
- Infliximab was associated with the highest risk of serious infections compared to adalimumab, etanercept, and abatacept. (moderate strength evidence)
    - There is moderate strength evidence that etanercept is associated with lower risk of serious infections compared to adalimumab.
- There is low strength evidence that shows that etanercept is associated with a lower risk of tuberculosis compared to infliximab and adalimumab.
- For herpes zoster, risk of malignancy, and mortality, low strength evidence suggests that there is no difference between etanercept, infliximab, and adalimumab.
- There is high strength evidence that suggests that combination therapy with two tumor necrosis factor inhibitor (TNFi) or one TNFi and another TIM with different mechanism of action is associated with an increased risk of adverse events compared to monotherapy with a TNFi.

Guidelines:

Rheumatoid Arthritis (RA):

- The American College of Rheumatology (ACR) recently updated their recommendations (2015) for biologic agents in treating RA and strongly recommended starting a TNFi (adalimumab, certolizumab pegol, etanercept, infliximab, or golimumab) or a non-TNF biologic (abatacept, rituximab, or tocilizumab) with or without methotrexate, in no particular order of preference, in RA that remains moderate or high despite disease-modifying antirheumatic drugs (DMARDs).[29]
- The ACR recommends starting a TNFi with or without methotrexate over tofacitinib monotherapy in RA that remains moderate or high despite DMARDs.[29]
    - This recommendation is conditional due to low quality evidence and shorter experience using tofacitinib.
- The European League Against Rheumatism (EULAR) recommend that if a patient's response to methotrexate or other DMARDs fails to achieve the treatment goal by 6 months or results in no improvement at 3 months, TIMs should be initaitied with methotrexate. TIMs to initiate include TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), abatacept, tocilizumab, or rituximab; there is no particular order of preference.[30]
- Clinical guidelines from the National Institute for Clinical Excellence (NICE) recommend that adalimumab, etanercept, and infliximab are options for adults with active RA and for those who have undergone trials of two DMARDS, including methotrexate (defined as 6 months).[31]

Targeted Immune Modulators (TIMs)

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Guidelines (cont):

Crohn's Disease (CD):

- The American College of Gastroenterology (ACG) recommend the use of TNFi (infliximab, adalimumab, and certolizumab pegol) for treatment of moderate to severe CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (grade A).[32]
    - Natalizumab is recommended for patients with moderate to severe CD that do not respond to conventional CD therapies and TNFi therapy (grade A).
- Clinical guidelines from the National Institute for Clinical Excellence (NICE) recommend that adalimumab and infliximab are options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy.[33]

Ulcerative Colitis (UC):

- The American College of Gastroenterology (ACG) recommend the use of infliximab in patients with moderate to severe UC that have failed therapy with corticosteroids and/or thiopurines.[34]
    - These guidelines are currently in the process of being updated.

Plaque Psoriasis (PP) or Psoriatic Arthritis (PA):

Current guidelines for plaque psoriasis and psoriatic arthritis recommend the use of TIMs in patients that have failed conventional therapies, but at this time the guidelines to not recommend one TIM over another.[35,36]

Juvenile Idiopathic Arthritis (JIA):

The ACR updated their recommendations (2013) for biologic agents in treating JIU and recommend the use of anakinra (off-label use) as initial therapy for patients with a physician global assessment (MD global) ≥5 irrespective of the active joint count (AJC), or an MD global <5 and an AJC >0 (level C). For patients with continued disease, ACR recommends abatacept following a trial of both an IL-1 inhibitor and tocilizumab (sequentially) (level D) or anakinra following treatment with glucocorticoid (level A) or NSAID monotherapy (level C). Additionally, TNFi is recommended for patients with an AJC >4 following a trial of an IL-1 inhibitor or tocilizumab (level C). The ACR states that use of a TNFi in patients with an AJC of 0 and an MD global <5, with exception of patients who have tried and failed treatment with an IL-1 inhibitor or tocilizumab, inappropriate (level D). The ACR recommends use of tocilizumab in patients with continued disease activity following glucocorticoid (level A), methotrexate or leflnomide (level B), or anakinra (level B) irrespective of the MD global and AJC.[37]

Antidrug Antibodies (ADAb):

- TNFi can elicit immunogenic response, including the emergence of antidrug antibodies (ADAb), which results in changes in pharmacokinetics. The development of ADAbs can effect drug concentrations, which in turn can cause the effectiveness of these agents to diminish in some patients over time.

- A large systematic review of 7969 patients with plaque psoriasis showed that ADAb against infliximab, etanercept, adalimumab, and ustekinumab were reported in 5.4-43.6%, 0-18.3%, 6-45%, and 3.8-6%, respectively. ADAb formation with infliximab and adalimumab were associated with lowered effectiveness. Whereas, ADAb formation due to etanercept was not linked to decreased treatment efficacy.[38]
- Patients with rheumatoid arthritis with an immunogenic response against a first TNFi (infliximab or adalimumab) were shown to have a better clinical response to a subsequent TNFi (etanercept) compared to patients with RA without ADAbs. In these patients, the response to the second TNFi did not differ from patients who were TNFi naïve.[39]

Targeted Immune Modulators (TIMs)

Rachael McCaleb, PharmD

December 14, 2015

Considerations:

- Include at least 2 TIMs as preferred
    - Remaining TIMS will be considered non-preferred (non-covered – NOT excluded)
- All FDA approved indications must be covered
- Must cover for JIA down to 2 years of age
- Must cover for CD down to 6 years of age
- Allow for grandfathering for current members on non-preferred agents
    - Preferred agents will be moved the T2
    - Current members on a non-preferred agent who switch to a preferred agent will receive the preferred agent for 4 months at a $0 copay
- Prior authorization criteria is non-negotiable
- Allow for price protection for the life of the contract
- Start date: New Contract

References:

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