MTF Formulary Management for Targeted Immunomodulatory Biologics (TIBs)

Defense Health Agency Pharmacy Operations Division
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Bottom-line:

- **Humira is the BCF and step-preferred agent; it has the most FDA-approved indications, the most clinical utility within the MHS, and is the most cost effective.**
- **The TIBs are now a BCF, rather than Extended Core Formulary (ECF) class. MTFs that currently don't have Humira on their formulary are required to add it to their local formularies.**
- **Prior Authorization applies to the class and Step Therapy now applies to new users of TIBs requiring a trial of the step-preferred Humira. Current users will be grandfathered.**
- **See chart on page 3 for the FDA approved indications and drugs in the class.**

Uniform Formulary Decision: The Director, DHA approved the recommendations from the August 2014 DoD P&T Committee meeting in November 2014, with an implementation date of February 18, 2015.

Uniform Formulary (UF) drugs		Non-Formulary (NF) drugs
BCF drugs - MTFs must have on formulary	**MTFs may have on formulary**	**MTFs must not have on formulary**
Step-preferred: Adalimumab (Humira)	**Non step-preferred:*** Apremilast (Otezla) Golimumab (Simponi) Tofacitinib (Xeljanz) Ustekinumab (Stelara)	**Non step-preferred:*** Abatacept (Orencia) Anakinra (Kineret) Certolizumab pegol (Cimzia) Etanercept (Enbrel) Tocilizumab (Actemra)
* Step therapy applies to new users – current users are grand-fathered		

Prior Authorization and Step Therapy information

- Current users of non-step preferred TIBs will be grandfathered.
- Automated (step therapy) prior authorization criteria apply to all new users of non-preferred TIBs, [abatacept (Orencia), anakinra (Kineret), apremilast (Otezla), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), tocilizumab (Actemra), tofacitinib (Xeljanz), and ustekinumab (Stelara)]. A trial of adalimumab (Humira) is required before the non-step preferred drugs.
- A trail of Humira is NOT required if the patient has had an inadequate response, intolerable adverse effects or contraindications to Humira or has previously responded to a non-formulary TIB and changing to Humira would incur unacceptable risk. A trial of Humira is NOT required in the following scenarios where there is no formulary alternative:
    i. Enbrel: patient has HCV
    ii. Non-TNF TIB (Orencia, Actemra, Xeljanz, Kineret, Stelara, and Otezla): Patient has symptomatic chronic heart failure
    iii. Actemra, Orencia or Simponi: Patient has been stable on an intravenous formulation, with continuous use in the past three months and needs to transition to the subcutaneous formulation
- Manual prior authorizations criteria are consistent with the FDA indications and apply to **all** users of TIBs.

Clinical Summary

- All the TIBs (adalimumab, etanercept, certolizumab, golimumab, abatacept, tocilizumab, tofacitinib, anakinra, ustekinumab and apremilast) are highly effective for their FDA indications vs. placebo, based on randomized controlled trials.
- There are few direct head-to-head trials between the TIBs. Comparative effectiveness is primarily determined though network meta-analysis (NMA) and indirect comparisons of of numbers needed to treat. The strength of evidence (SOE) is typically low.

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Rheumatoid Arthritis

- There is insufficient evidence to clearly show superiority of one TIB over another with regard to the American College of Rheumatology 50 (ACR50) endpoint for response to treatment.
- In three systematic reviews, anakinra had a lower mean response when compared to etanercept and adalimumab (Humira).

Psoriatic Arthritis & Psoriasis

- For psoriatic arthritis (PsA), due to the lack of head-to-head clinical trials and heterogeneous study populations, there is insufficient evidence to determine comparative efficacy between the four anti-TNFs (adalimumab, certolizumab, etanercept, and golimumab) and ustekinumab and apremilast.
- For psoriasis (PsO), three products are approved: adalimumab, etanercept and ustekinumab. In one head-to-head RCT, ustekinumab was superior to etanercept in achieving response, based on the Psoriasis Activity and Severity Index 75 (PASI 75) score. A NMA demonstrated similar efficacy for adalimumab and ustekinumab.

Inflammatory Bowel Disease

- For Crohn's Disease (CD), a NMA demonstrated that adalimumab and certolizumab are both effective for the induction of response and maintenance of remission and response. The same analysis showed adalimumab is superior to certolizumab for induction of remission.
- For ulcerative colitis (UC), there is insufficient data for direct comparison of adalimumab and golimumab.

Safety and Tolerability

- The overall rates of adverse events (AEs) are similar among all the TIBs.
- Indirect comparisons suggest the rate of serious infections is higher with certolizumab than other TIBs. In a sub-group analysis, all the anti-TNF drugs except etanercept were associated with an increased risk of serious infections compared to controls.
- Low SOE suggests the risk of malignancy with the TIBs is not increased. The risk of nonmelanoma skin cancer is increased with the anti-TNF drugs (adalimumab and etanercept) compared to other TIBs.
- The non-TNF biologics have some unique safety concerns such as laboratory abnormalities and GI perforation (tocilizumab and tofacitinib); Depression and suicidal ideations (apremilast); and increased risk of exacerbation in adults with chronic obstructive pulmonary disease (abatacept).
- Concurrent use of two TIBs results in increased AEs and is contraindicated.

TIB Price Comparison at MTF

Drug & Dosage Form	MTF cost/month (Aug 2014)	
Basic Core Formulary		
Adalimumab (Humira)	$	**Most Cost-Effective**
Uniform Formulary		
Apremilast (Otezla)	$$	**Less Cost-Effective**
Golimumab (Simponi)	$$	**Less Cost-Effective**
Tofacitinib (Xeljanz)	$$	**Less Cost-Effective**
Ustekinumab (Stelara)	$$$	**Lesser Cost-Effective**
Non-Formulary		
Abatacept (Orencia)	$$$	**Lesser Cost-Effective**
Anakinra (Kineret)	$$	**Less Cost-Effective**
Certolizumab (Cimzia)	$$$$	**Least Cost-Effective**
Etanercept (Enbrel)	$$	**Less Cost-Effective**
Tocilizumab (Actemra)	$$$	**Lesser Cost-Effective**

References

- DoD P&T Committee minutes: http://pec.ha.osd.mil/pt_minutes.php?submenuheader=5
- Current/future drug classes under review by the DoD P&T Committee: http://pec.ha.osd.mil/PT_Committee.php?submenuheader=4
- TRICARE formulary search tool: http://pec.ha.osd.mil/formulary_search.php?submenuheader=1
- Prior Authorization/Medical Necessity forms: http://pec.ha.osd.mil/forms_criteria.php?submenuheader=1
- Point of contact for additional information: usarmy.jbsa.medcom-ameddcs.list.pecuf2@mail.mil

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Generic	Brand	Mfg	MoA	Frequency	Other	Rheum				Derm	Gastro	
						RA	JIA	AS	PsA	Plaque Psoriasis	Crohn's	UC
Adalimumab	**Humira**	**Abbott**	**TNF**	**SQ (qow-qw)**		X	≥2 yr	X	X	X	≥ 6 yr	X
Certolizumab	Cimzia	UCB	TNF	SQ (qow-qmo)		X		X	X		X	
Etanercept	Enbrel	Amgen	TNF	SQ (qwk)		X	≥ 2 yr	X	X	X		
Golimumab	Simponi	J&J	TNF	SQ (qmonth)	*w/ MTX	X*		X	X			X
Abatacept	Orencia	BMS	CTLA4	SQ (q week)	DMARD-IR	X						
Tocilizumab	Actemra	Roche	IL6	SQ (qow-qwk)		X						
Tofacitinib	Xeljanz	Pfizer	JAK	PO BID	MTX-IR	X						
Anakinra	Kineret	Amgen	IL1	SQ (qday)	NOMID, Gout	X						
Ustekinumab	Stelara	J&J	IL12	SQ (q 2 wks)					X	X		
Apremilast	Otezla	Celgene	PDE-4	PO BID					X	X		

RA = rheumatoid arthritis; JIA = juvenile idiopathic arthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; UC = ulcerative colitis; NOMID = neonatal onset multisystem inflammatory disease; CAPS = cryopyrin- associated periodic syndromes

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