



Therapeutic Class ReviewSM

Biological Response Modifiers – adalimumab (Humira[®]) Update – Psoriasis & Crohn's Disease

April 2008

New Product for Review:
Adalimumab (Humira[®]) [Abbott]

Dossier Provided by Manufacturer: No
Dossier Evaluation: N/A

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Executive Summary

Disease State Background

- **Psoriasis** is a common, non-contagious chronic inflammatory skin condition with significant physical and psychosocial morbidity.
 - Chronic plaque psoriasis is the most common form, accounting for 85 to 90% of cases.
 - Although not usually life threatening, the disabilities of living with psoriasis are similar to or exceed those of other major illnesses such as diabetes, arthritis and cancer.^[25]
 - There is no cure for psoriasis. Current treatments include topical (locally applied) preparations, phototherapy and systemic (whole body) treatments. Although topical treatments are the mainstay of psoriasis management, 20 to 30% of people with psoriasis have severe enough disease to require either systemic treatment or phototherapy
 - The Psoriasis Area and Severity Index (PASI) score remains the most accepted and widely used severity scoring in clinical trials.
 - The clinical features of psoriasis (i.e., erythema, scale, and surface area) are graded and incorporated into a single score which can range from 0 to 72.
 - A reduction of baseline PASI score of 75%, termed a PASI 75, is widely used, particularly by the FDA and pharmaceutical companies, as the benchmark of primary end-points in assessing therapies for psoriasis.
- **Crohn's disease** is a transmural inflammatory disorder which can involve any part of the gastrointestinal tract and which is characterized by chronicity, recurrences and numerous complications.
 - There is no cure for Crohn's disease, and treatment regimens are directed toward inducing remission, maintaining remission and addressing complications.
 - The Crohn's Disease Activity Index (CDAI) is a research tool used to quantify the symptoms of patients with Crohn's disease.

- Remission of Crohn's disease is defined as a fall in the CDAI of less than 150. Severe disease was defined as a value of greater than 450. Most major research studies on medications in Crohn's disease define response as a fall of the CDAI of greater than 70 points. There is no absolute upper end to this assessment tool.

Biologic Treatment Options

- Adalimumab (Humira) is a biological agent approved in December 2002 for the treatment of rheumatoid arthritis.
 - It is a recombinant human IgG 1 monoclonal antibody specific for human tumor necrosis factor (TNF).
 - It binds specifically to TNF- α and blocks its interaction with cell surface TNF receptors.
- Since coming to market, it has been approved for psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and most recently, psoriasis and juvenile idiopathic arthritis.
 - The FDA approved adalimumab (Humira) for Crohn's disease in February 2007.
 - Approval for moderate-to-severe psoriasis occurred in January 2008.
 - Approval for idiopathic juvenile arthritis (juvenile rheumatoid arthritis) occurred in February 2008.

Comparison of FDA-approved indications for biologic immunomodulators used for psoriasis and/or Crohn's disease.

Drug	Formulary Status	Moderate-to-Severe Psoriasis	Moderate-to-Severe Crohn's disease	Idiopathic Juvenile Arthritis
etanercept (Enbrel)	F	✓	-	✓
adalimumab (Humira)	NF	✓	✓	✓
efalizumab (Raptiva)	NF	✓	-	-
infliximab (Remicade)	Med	✓	✓	-
alefacept (Amevive)	Med	✓	-	-
natalizumab (Tysabri)	Med	-	✓	-

F=formulary, NF=non-formulary, Med=covered under medical benefit

- Currently, preferred/formulary biologic alternatives for psoriasis and Crohn's disease include:
 - Psoriasis:
 - Etanercept (Enbrel) is our only preferred/formulary self-administered biologic indicated for the treatment of moderate-to-severe psoriasis.
 - Infliximab (Remicade) and alefacept (Amevive) are administered by IV infusion in a controlled health care setting and are available under the medical benefit.
 - Efalizumab (Raptiva) is a self administered biologic that inhibits T-cell migration into the skin and is non-preferred/non-formulary.
 - Crohn's Disease
 - There are currently no preferred/formulary self-administered biologics indicated for the treatment of Crohn's disease.
 - Infliximab (Remicade) and natalizumab (Tysabri) are covered under the medical benefit.

Evidence

- There is possibly useful evidence that adalimumab (Humira) is effective in the management of moderate-to-severe psoriasis.
 - At 16 weeks, the NNT to achieve PASI 75 was two.

- There is possibly useful evidence that etanercept (Enbrel) is effective in the management of moderate-to-severe psoriasis.
 - At 12 weeks, the NNT to achieve PASI 75 with etanercept (Enbrel) was 3.
- There are no head-to-head trials comparing adalimumab (Humira) with etanercept (Enbrel) for the treatment of moderate-to-severe psoriasis.
- There is possibly useful evidence that adalimumab (Humira) is effective in inducing remission (CDAI score < 150) in patients with moderate-to-severe Crohn’s disease.
- There is no useful evidence that adalimumab (Humira) has a different safety profile from other TNF- α inhibitors, such as etanercept (Enbrel) or infliximab (Remicade).
 - Adalimumab (Humira) and infliximab (Remicade) carry “black-box” warnings for the risk of serious infections and tuberculosis.
 - Infliximab (Remicade) carries an additional “black-box” warning for Hepatosplenic T-Cell Lymphomas.
 - Etanercept (Enbrel) carries no “Black-box” warnings, but does carry bolded warnings for serious infections and sepsis, as well as tuberculosis.

Decision

Adalimumab (Humira) is preferred/formulary because:

- There is reliable information that adalimumab (Humira) is effective in the management of moderate-to-severe plaque psoriasis, with efficacy and safety at least comparable to currently available preferred/formulary alternatives.
- There is reliable information that adalimumab (Humira) is effective in inducing remission in patients with moderate-to-severe Crohn’s disease, and is the only self-administered biologic available for this indication.

Products ^[3-5]

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^d
etanercept (Enbrel [®])	11/98	N/A	<ul style="list-style-type: none"> • Rheumatoid Arthritis • Juvenile Rheumatoid Arthritis • Psoriatic Arthritis • Ankylosing spondylitis 	50 mg SC every week	<ul style="list-style-type: none"> • Bone metastasis - Pain from metastases • Graft versus host disease • Hemophagocytic lymphohistiocytosis, Reactive • Hidradenitis suppurativa, Severe, refractory • Langerhans cell histiocytosis • Myelosclerosis with myeloid metaplasia • Nephrotic syndrome
			<ul style="list-style-type: none"> • Moderate-to-severe plaque psoriasis 	50 mg SC twice weekly x 3 months, then 50 mg weekly	

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^d
					<ul style="list-style-type: none"> • Pemphigoid • Sarcoidosis • TNF receptor-associated periodic fever syndrome (TRAPS)
adalimumab (Humira)	12/02	N/A	<ul style="list-style-type: none"> • Rheumatoid Arthritis • Psoriatic Arthritis • Ankylosing spondylitis 	40 mg SC every other week up to 40 mg SC every week	<ul style="list-style-type: none"> • None listed
			<ul style="list-style-type: none"> • Crohn's Disease 	160 mg SC week 0, 80 mg SC week 2, then 40 mg SC every other week	
			<ul style="list-style-type: none"> • Moderate-to-severe plaque psoriasis 	80 mg SC on week 0, then 40 mg SC every other week	
efalizumab (Raptiva [®])	10/03	N/A	<ul style="list-style-type: none"> • Moderate-to-severe plaque psoriasis 	0.7 mg/kg x 1 dose, then 1 mg/kg SC each week	<ul style="list-style-type: none"> • Severe atopic dermatitis
infliximab (Remicade [®])	08/98	N/A	<ul style="list-style-type: none"> • Rheumatoid Arthritis 	3 mg/kg IV every 8 weeks up to 10 mg/kg every 4 weeks	<ul style="list-style-type: none"> • Arthritis - Arthropathy in Crohn's disease • Behçet's syndrome • Gastrointestinal tract transplanted organ rejection • Giant cell arteritis • Graft versus host disease • Hidradenitis suppurativa, Severe, refractory • Inflammatory bowel disease • Juvenile chronic arthritis • Juvenile idiopathic arthritis (Severe), Refractory to other therapies • Necrobiosis lipoidica diabetorum • Pyoderma gangrenosum • SAPHO
			<ul style="list-style-type: none"> • Ankylosing Spondylitis 	5 mg/kg IV every 6 weeks	
			<ul style="list-style-type: none"> • Crohn's Disease • Psoriatic Arthritis • Plaque Psoriasis • Ulcerative Colitis 	5 mg/kg IV every 8 weeks	

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^d
					syndrome Refractory <ul style="list-style-type: none"> • Sarcoidosis • Sprue, Refractory • Subcorneal pustular dermatosis • Systemic onset juvenile chronic arthritis • Wegener's granulomatosis, Refractory, in combination with corticosteroids
alefacept (Amevive [®])	1/2003	N/A	<ul style="list-style-type: none"> • Plaque psoriasis 	15 mg IM once weekly X 12 weeks (MR x 1)	<ul style="list-style-type: none"> ▪ Psoriatic arthritis

^a Date applies to approval date for the original brand name medication where there are now generics available.

^c Based on patents listed in Orange Book as of 01/2008.

^d As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

References

1. Klasco RK (Ed): DRUGDEX[®] System (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at: <http://www.thomsonhc.com> (cited: 11/1/07)
2. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2006. Available from Wolters Kluwer Health, Inc. Accessed November 1, 2007.
3. Humira[®] [package insert]. North Chicago, IL: Abbott Laboratories; January 2008
4. Enbrel[®] [package insert]. Thousand Oaks, CA: Immunex Corporation; October 2007
5. Remicade[®] [package insert]. Malvern, PA: Centocor, Inc.; April 2007
6. Menter A, Tying SK, Gordon K, et al. Adalimumab therapy for moderate-to-severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008 Jan;58(1):106-15.
7. Saurat JH, Stingl G, Dubertret L, et al.; for the CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2007 Nov 28; [Epub ahead of print]
8. Leonardi CL, Powers JL, Matheson RT, et al.; Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003 Nov 20;349(21):2014-22.
9. Papp KA, Tying S, Lahfa M, et al.; Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005 Jun;152(6):1304-12.
10. Tying S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet*. 2006 Jan 7;367(9504):29-35.
11. Tying S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol*. 2007 Jun;143(6):719-26.
12. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006 Feb;130(2):323-33;
13. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med*. 2007 Jun 19;146(12):829-38.
14. Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate-to-severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol*. 2006 Oct;55(4):598-606.
15. Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol*. 2003 Dec;139(12):1627-32;
16. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007 Jan;132(1):52-65.
17. Cassano N, Loconsole F, Galluccio A, Miracapillo A, Pezza M, Vena GA. Once-weekly administration of high-dosage Etanercept in patients with plaque psoriasis: results of a pilot experience (power study). *Int J Immunopathol Pharmacol*. 2006 Jan-Mar;19(1):225-9.
18. Moore A, Gordon KB, Kang S, et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. *J Am Acad Dermatol*. 2007 Apr;56(4):598-603.
19. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007 Sep;56(9):1232-9. Epub 2007 Feb 13.
20. Hanauer SB, Feagan BG, Lichtenstein GR, et al.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002 May 4;359(9317):1541-9.
21. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. 2006 Mar;130(3):935-9.
22. National Institute for Health and Clinical Excellence (NICE). Etanercept and efalizumab for the treatment of adults with psoriasis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jul. 35 p. (Technology appraisal guidance; no. 103).
23. Guyatt GH, Mitchell A, Irvine EJ et al. A new measure of health status for clinical trials in Inflammatory Bowel Disease. *Gastroenterology* 1989, 96:804-810.
24. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD006893. DOI: 10.1002/14651858.CD006893.
25. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol*. 1999 Sep;41(3 Pt 1):401-7.