



Therapeutic Class ReviewSM

Biologic Response Modifiers – rilonacept (Arcalyst[®])

October 2008

New Product for Review:

Rilonacept (Arcalyst[®]) [Regeneron]

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

Cryopyrin-Associated Periodic Syndromes (CAPS) ^[1,7,8]

- Cryopyrin-associated periodic syndromes (CAPS) are a group of rare genetic diseases affecting approximately 200 to 300 people in the United States, attributed to mutations in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1) gene. CIAS1 encodes for cryopyrin, a protein that controls activation of an inflammatory cytokine, interleukin-1 (IL-1). CIAS1 is sometimes referred to as the NLRP-3 gene.
- The syndromes of CAPS include Familial Cold Auto-Inflammatory Syndrome (FCAS), Muckle Wells Syndrome (MWS), and Neonatal-Onset Multisystem Inflammatory Disease (NOMID). FCAS is the mildest and most common of the three syndromes.
- The pathogenesis of CAPS is believed to be related to uncontrolled overproduction and release of IL-1 with resultant inflammation.
- Clinical symptoms usually first present in early childhood and appear similar to presentation of the flu or allergy. However, more serious cases experience hearing impairment or deafness, increased intra-cranial pressure, joint abnormalities/pain and renal impairment.
- Diagnosis is typically based on symptoms described above, family history and lab findings consistent with inflammatory disease (C-reactive protein and serum amyloid A) without signs of infection. Although CAPS are described as a genetic disorder, genetic testing is of uncertain usefulness to confirm diagnosis because not all patients are CIAS1 (NLRP-3) mutation positive. However, all subject in the Arcalyst clinical trial tested positive for CIAS1 mutation.
- Anecdotal reports and a published retrospective case series suggest IL-1 inhibition with anakinra (Kineret) may be an effective treatment for CAPS. ¹¹

Rilonacept (Arcalyst)

- Rilonacept (Arcalyst) is a biologic agent given once weekly by subcutaneous injection.
- It inhibits the inflammatory effects of interleukin-1 (IL-1) by acting as a soluble decoy receptor, binding circulating IL-1 before it can interact with cell surface receptors.
- Rilonacept (Arcalyst) was approved in February 2008 under the Orphan Drug Act for the treatment of CAPS.^[5] Approval was based on a priority review of one 24-week clinical trial in 46 subjects evaluating the superiority of rilonacept (Arcalyst) in reducing disease symptoms compared to placebo.
- There is potential for off-label use in more common diseases such as rheumatoid arthritis, refractory gout, and coronary artery disease; these conditions were studied in the rilonacept (Arcalyst) clinical development program.^[6]
- Because symptoms of CAPS are also commonly seen in patients with allergies and flu, there is some likelihood rilonacept (Arcalyst) may be used in unconfirmed cases.

Evidence^[1]

- One randomized, multiphase clinical trial evaluated the efficacy and safety of rilonacept (Arcalyst) in a total of 46 CAPS subjects.
- This trial was critiqued as unreliable for making healthcare decisions due to several flaws, including:
 - Some subjects received the wrong treatment for a few weeks during the trial.
 - Subjects used other drugs that could affect symptoms measured by DHAF (primary outcome measure).
 - The primary outcome measure is subjective and does not provide a clinical guide to assigning values nor does it provide insight on clinically meaningful benefit.

Safety^[1,2]

- Mild-to-moderate injection site reactions lasting approximately one day are common after the injection of rilonacept (Arcalyst).
- Rilonacept (Arcalyst) should not be used in patients with a chronic or active infection.
- No serious infections were seen during the pivotal trial. However, two patients receiving rilonacept (Arcalyst) have experienced serious infection (one resulting in death), so its use is associated with increased risk of serious infection.

Decision

Rilonacept (Arcalyst) is non-preferred/non-formulary because:

- The evidence for the safety and efficacy of this medication is uncertain.
- There is some low quality evidence to suggest that anakinra (Kineret) is effective in the treatment of CAPS. Given the availability of this product at a much lower cost, anakinra (Kineret) might provide a better treatment alternative for some CAPS patients.

Products

Table 1. Available Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^{d,1,6}
Rilonacept (Arcalyst)	2/2008	Not applicable to biologics	CAPS (FCAS and MWS)	Adults: 320mg loading dose, followed by 160mg once weekly by subcutaneous injection Children, 12-17: loading dose of 4.4 mg/kg, followed by 2.2mg/kg once weekly by subcutaneous injection	Rheumatoid arthritis, coronary heart disease, juvenile idiopathic arthritis, gout, Still's disease
Anakinra (Kineret)	10/2001	Not applicable to biologics	Rheumatoid arthritis	Adults: 100mg daily by subcutaneous injection Children: not for use in kids	CAPS

^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 04/09/2008.

^d As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.

Table 2. Products in development

Drug Products	Development status ^a	Regulatory status	Potential Indications	Usual Dose/Route	Development plan ^a
ACZ 885 [IL-1 antagonist]	Pivotal trial (NCT 00465985) due to complete in September 2008. Follow up safety trial (NCT00685373) not yet recruiting	Novartis plans filing in 2009 as a new molecular entity. ^b	In development for treatment of FCAS, MWS and NOMID.	Given as subcutaneous injection every 8 weeks	Ongoing trials in these additional disease states: RA, COPD, NIDDM
Anakinra (Kineret) [IL-1 antagonist]	Phase 1 (NCT00214851) completed 12/2005	TBD	In development for treatment of FCAS?	Given as a once daily subcutaneous injection	FDA approved for treatment of RA.
anakinra (Kineret) [IL-1 antagonist]	Phase 2 (NCT00069329) recruiting	TBD	In development for treatment of NOMID	Given as a once daily subcutaneous injection	FDA approved for treatment of RA.

^a Clinical Trials.gov. [database on the internet]. Available at <http://clinicaltrials.gov/ct2/show/NCT00465985?intr=%22ACZ885%22&rank=5>. Accessed July 14, 2008. and August 20, 2008.

^b New products in development [page on the internet]. Available at <http://www.novartis.com/research/pharmaceutical-product.shtml>. Accessed July 14, 2008.

References

1. Drugs@FDA [page on the internet]. FDA review documents for riloncept (Arcalyst). Available at: <http://www.fda.gov/cder/foi/nda/2008/125249s000TOC.htm>. Accessed 05/15/2008.
2. Arcalyst (riloncept) prescribing information. Regeneron Pharmaceuticals, Tarrytown, NY, February 2008.
3. Arcalyst (riloncept) injection for subcutaneous use in the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS). [CD-ROM]. Regeneron Pharmaceuticals; 2008. Reviewed May 2008.
4. Cryopyrin-Associated Periodic Syndromes (CAPS) and its impact on patients. [CD-ROM]. Regeneron Pharmaceuticals; 2008. Reviewed May 2008.
5. FDA approves new orphan drug for treatment of rare inflammatory syndromes. News Release available at <http://fda.gov/bbs/topics/NEWS/2008/NEW01801.html>. Accessed March 20, 2008.
6. Arcalyst studies. Available at <http://clinicaltrials.gov/ct2/results?term=arcalyst>. Accessed March 27, 2008.
7. Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. *Clin Exp Dermatol*. 2008 Jan;33(1):1-9.
8. UpToDate 15.1 [online]. 2007. Available at <http://www.uptodate.com>. Accessed March 20, 2008.
9. Hoffman H, Mellis S, Grimes I, et al. Variability of disease activity in cryopyrin-associated period syndromes (CAPS): design of a daily health assessment form (DHAF) for clinical research. *Arthritis Rheum*. 2007;56(9) Supplement: Abstract 168.
10. Hoffman HM, Throne ML, Amar NJ, et al. Efficacy and safety of riloncept (interleukin-1 trap) in patients with cryopyrin-associated periodic syndromes: Results from two sequential placebo-controlled studies. *Arthritis Rheum* 2008 Aug;58(8):2443-52.
11. Leslie KS, Lachmann HJ, Bruning E. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1?NALP3 mutations.