Division Director and Cross-Discipline Team Leader Review
BLA 125057/S408

Date	September 28, 2018
From	Wiley A. Chambers, M.D.; William M. Boyd, M.D.
Subject	Division Director and Cross-Discipline Team Leader Review
BLA # and Supplement#	125057/S408
Applicant	AbbVie Inc.
Date of Submission	December 5, 2017
PDUFA Goal Date	October 5, 2018
Proprietary Name	Humira
Established or Proper Name	Adalimumab
Dosage Form(s)	Injection: 40 mg/0.8 mL in a single-use prefilled pen Injection: 40 mg/0.4 mL in a single-use prefilled pen Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe Injection: 40 mg/0.4 mL in a single-use prefilled glass syringe Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe Injection: 10 mg/0.2 mL in a single-use prefilled glass syringe Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use
Regulatory Action	Approval
Indication(s)/Population(s)	Treatment of non-infectious intermediate, posterior and panuveitis in pediatric patients 2 years of age and older
Recommended Dosing Regimen(s)	• *10 kg (22 lbs) to <15 kg (33 lbs):* 10 mg every other week • *15 kg (33 lbs) to < 30 kg (66 lbs):* 20 mg every other week • *≥ 30 kg (66 lbs):* 40 mg every other week

1. Benefit-Risk Assessment

BLA 125057/S-397 Humira (adalimumab) will be approved for the treatment of non-infectious intermediate, posterior and panuveitis in pediatric patients 2 years of age and older.

The safety and effectiveness of Humira for the treatment of non-infectious uveitis have been established in pediatric patients 2 years of age and older. The use of Humira is supported by evidence from adequate and well-controlled studies of Humira in adults and a 2:1 randomized, controlled clinical study in 90 pediatric patients. The safety and effectiveness of Humira has not been established in pediatric patients with uveitis less than 2 years of age.

Humira has been studied in 464 adult patients with uveitis (UV) in placebo-controlled and open-label extension studies and in 90 pediatric patients with uveitis (Study PUV-I). The safety profile for patients with UV treated with Humira was similar to the safety profile seen in patients with RA.

2. Background

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody for human tumor necrosis factor (TNF)-α. Tumor necrosis factor (TNF) is a cytokine that is involved in normal inflammatory and immune responses including non-infectious uveitis. Elevated levels of TNF are thought to play a role in autoimmune disorders and immune-mediated disorders. Adalimumab is believed to decrease the inflammatory process by binding to TNF-alpha and blocking its interaction with cell surface TNF receptors.

Adalimumab was first approved for the treatment of rheumatoid arthritis in the United States in December 2002 and subsequently has been approved for the following indications: Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, and Uveitis.

In April 2016, the applicant sought guidance on using the SYCAMORE[1] study conducted in the United Kingdom (UK) to support a pediatric uveitis indication. The applicant was asked to submit the results of the study during the review cycle of supplement 397 which was under review.

In June 2016, Supplement 397 was approved for the treatment of noninfectious, intermediate, posterior and panuveitis in adult patients. The applicant did not submit the pediatric study, nor ask for approval in pediatric uveitis patients in Supplement 397. The applicant did not submit a pediatric plan prior to the submission of supplement 397, but did receive orphan designation for the treatment of treatment of non-infectious intermediate, posterior and panuveitis and therefore was not required to submit a pediatric plan.

3. Product Quality

There is no information in this supplement indicating any change to the approved CMC procedures for adalimumab drug substance and drug product.

4. Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology studies were performed for this supplement.

5. Clinical Pharmacology

No new Clinical Pharmacology studies were performed for this efficacy supplement.

[1] A Randomized Controlled Trial of the Clinical Effectiveness, Safety and Cost Effectiveness of Adalimumab in Combination with Methotrexate for the Treatment of Juvenile Idiopathic Arthritis Associated Uveitis

6. Clinical Microbiology

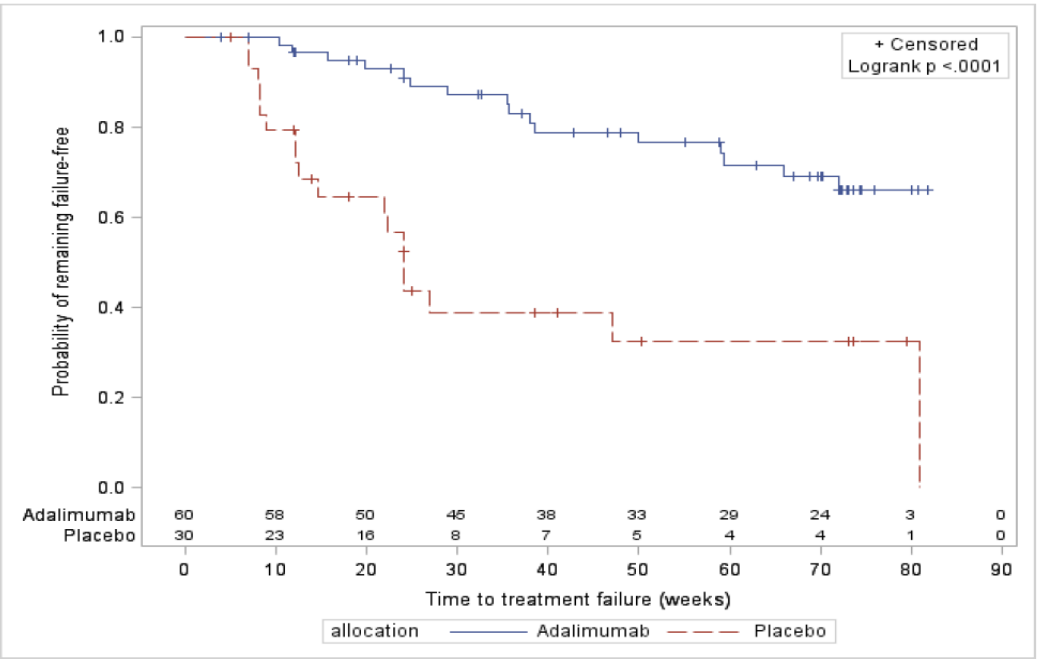
Not applicable. This is not an anti-infective product.

7. Clinical/Statistical- Efficacy

From the Medical Officer's review finalized 9/10/2018:

SYCAMORE was a randomized, double-masked, placebo-controlled, multicenter, trial of adalimumab in combination with methotrexate in patients with active uveitis in association with juvenile idiopathic arthritis refractory to methotrexate monotherapy. The primary objective was to compare the clinical effectiveness of adalimumab in combination with methotrexate versus placebo in combination with methotrexate, with regard to controlling disease activity in refractory uveitis associated with juvenile idiopathic arthritis. Patients were randomized using a 2:1 ratio to receive either adalimumab via subcutaneous (SC) injection every two weeks for 18 months or a placebo SC injection every two weeks for 18 months, both treatment groups also received MTX in combination with their allocated treatment. The standard of care in UK is treatment with Methotrexate - therefore, the control was maintained on MTX while the intervention was allocated in a placebo-controlled fashion. Following the completion of the treatment period, patients were followed up for an additional six months. The primary efficacy endpoint for the trial was "time to treatment failure".

Figure 1: Kaplan Meier Plot for time to treatment failure



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Module 5.3.5.1 CSR page 113

Table 1: Quartile Estimates for time to treatment failure - Placebo

Quartile Estimates				
	Point	95% Confidence Interval		
Percent	Estimate	Transform	[Lower	Upper)
75	81.0000	LOGLOG	24.1429	81.0000
50	24.1429	LOGLOG	12.4286	81.0000
25	12.1429	LOGLOG	8.0000	22.2857

Module 5.3.5.1 CSR page 107

Table 2: Quartile Estimates for time to treatment failure – Adalimumab

Quartile Estimates				
	Point	95% Confidence Interval		
Percent	Estimate	Transform	[Lower	Upper)
75	.	LOGLOG	.	.
50	.	LOGLOG	72.0000	.
25	59.0000	LOGLOG	28.8571	.

Module 5.3.5.1 CSR page 107

The study met its primary efficacy endpoint demonstrating a statistically significant difference between adalimumab/methotrexate and placebo/methotrexate in the time to treatment failure. The median time to treatment failure in the placebo group was 24.1 weeks. The median time in the adalimumab group was > 18 months (total study duration).

The currently approved dosing for pediatric patients with JIA is 10 mg every other week (EOW) in patients 10-15kg, 20 mg EOW in patients 15-30 kg and 40 mg EOW in patients > 30 kg. The Sycamore study used a slightly modified alternative dosing method (20 mg for participants weighing <30 kg or 40 mg for participants weighing >30 kg) based on PK modeling and a study conducted by Lovell and published in 2008. The sponsor proposed (b) (4)

8. Safety

From the Medical Officer's review finalized 9/10/2018:

Extent of Exposure

	Placebo N=30	Adalimumab N=60
Total number of doses received		
Mean (SD)	9.63 (9.68)	21.12 (11.98)
Median (min – max)	6 (1 - 39)	20.50 (1 – 40)
Duration of treatment (days)		
Mean (SD)	151.57 (150.34)	315.85 (173.77)
Median (min – max)	87 (14 - 571)	322 (14 – 561)
Duration of treatment (days) (n[%])		
1-28	6 (20.0%)	3 (5.00%)
29-56	5 (16.67%)	3 (5.00%)
57-112	7 (23.33%)	5 (8.33%)
113-168	2 (6.67%)	4 (6.67%)
169-224	3 (10.00%)	4 (6.67%)
225-280	2 (6.67%)	9 (15.0%)
281-336	2 (6.67%)	4 (6.67%)
337-392	0 (0%)	4 (6.67%)
393-448	1 (3.33%)	3 (5.00%)
449-504	0 (0%)	11 (18.33%)
≥ 505	2 (6.67%)	10 (16.67%)

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Module 5.3.5.1 CSR page 195

Deaths

There were no deaths during the course of this trial.

Nonfatal Serious Adverse Events

Treatment Group	Subject Number	Age	Sex	MedDRA PT
Adalimumab (N=60)				
	(b) (6)	4	Female	Varicella
		3	Female	Streptococcal infection
		7	Male	Diarrhea, Syncope
		5	Female	Viral infection
		9	Male	Scarlet fever
		9	Female	Cellulitis, Infected bites
		5	Female	Lower respiratory tract infection
		9	Female	Cataract
		5	Female	Varicella
		14	Male	Testes exploration

Treatment Group	Subject Number	Age	Sex	MedDRA PT
	(b) (6)	6	Male	Streptococcal infection
		7	Female	Viral infection
		8	Female	Antiviral prophylaxis
		7	Male	Food poisoning
		6	Male	Tonsillar hypertrophy
Placebo (N=30)				
	(b) (6)	7	Female	Anterior chamber flare
		6	Male	Uveitis

Module 5.3.5.1 CSR page 205

The rate of serious adverse events was approximately 3 times higher in the adalimumab group versus the placebo group [15/60 (25%) versus 2/30 (7%)]. Most of the serious adverse events in the adalimumab group are due to infections. Infections are a known event associated with adalimumab and adequately addressed in the label.

Common Adverse Events (Adverse Events Reported in ≥ 5% of Subjects in the Adalimumab Group)

	Adalimumab	Placebo	Total
Blood and lymphatic system disorders			
Lymphadenopathy	3 (5%)	0 (0%)	3 (3.3%)
Eye disorders			
Eye pain	4 (6.7%)	0 (0%)	4 (4.4%)
Gastrointestinal disorders			
Abdominal pain	3 (5%)	0 (0%)	3 (3.3%)
Diarrhea	8 (13.3%)	1 (3.3%)	9 (10%)
Nausea	5 (8.3%)	2 (6.7%)	7 (7.8%)
Vomiting	18 (30%)	5 (16.7%)	23 (25.6%)
General disorders and administration site conditions			
Injection site erythema	3 (5%)	1 (3.3%)	4 (4.4%)
Injection site mass	3 (5%)	0 (0%)	3 (3.3%)
Injection site pain	5 (8.3%)	2 (6.7%)	7 (7.8%)
Injection site pruritus	3 (5%)	0 (0%)	3 (3.3%)
Injection site reaction	7 (11.7%)	0 (0%)	7 (7.8%)
Injection site swelling	4 (6.7%)	1 (3.3%)	5 (5.6%)
Pyrexia	12 (20%)	2 (6.7%)	14 (15.6%)
Infections and infestations			
Ear infection	6 (10%)	2 (6.7%)	8 (8.9%)
Impetigo	3 (5%)	1 (3.3%)	4 (4.4%)
Lower respiratory tract infection	8 (13.3%)	2 (6.7%)	10 (11.1%)
Nasopharyngitis	15 (25%)	7 (23.3%)	22 (24.4%)
Oral herpes	3 (5%)	1 (3.3%)	4 (4.4%)

Paronychia	3 (5%)	1 (3.3%)	4 (4.4%)
Pharyngitis	4 (6.7%)	0 (0%)	4 (4.4%)
Tonsillitis	12 (20%)	0 (0%)	12 (13.3%)
Upper respiratory tract infection	4 (6.7%)	1 (3.3%)	5 (5.6%)
Urinary tract infection	9 (15%)	3 (10%)	12 (13.3%)
Varicella	3 (5%)	0 (0%)	3 (3.3%)
Viral infection	13 (21.7%)	1 (3.3%)	14 (15.6%)
Injury, poisoning and procedural complications			
Fall	3 (5%)	0 (0%)	3 (3.3%)
Investigations			
Alanine aminotransferase increased	4 (6.7%)	1 (3.3%)	5 (5.6%)
Aspartate aminotransferase increased	3 (5%)	1 (3.3%)	4 (4.4%)
Intraocular pressure increased	4 (6.7%)	0 (0%)	4 (4.4%)
Musculoskeletal and connective tissue disorders			
Arthralgia	12 (20%)	2 (6.7%)	14 (15.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma	5 (8.3%)	0 (0%)	5 (5.6%)
Nervous system disorders			
Headache	12 (20%)	4 (13.3%)	16 (17.8%)
Respiratory, thoracic and mediastinal disorders			
Cough	22 (36.7%)	3 (10%)	25 (27.8%)
Epistaxis	3 (5%)	0 (0%)	3 (3.3%)
Oropharyngeal pain	16 (26.7%)	2 (6.7%)	18 (20%)
Skin and subcutaneous tissue disorders			
Rash	3 (5%)	1 (3.3%)	4 (4.4%)

Module 5.3.5.1 CSR page 201

Adverse events are higher in the adalimumab group versus placebo and occur at a rate ≥ 5% in the adalimumab group. This cut-off is used to be able to compare the currently labeled adverse event rate with those seen in the uveitis program. The types of adverse events that occurred during this development program are adequately addressed in the current label.

9. Advisory Committee Meeting

There were no issues raised during the review of this supplemental application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

As a new indication, this application would have triggered PREA except that the applicant received orphan status designation and therefore was exempt from the requirements of PREA. The applicant obtained access to the SYCAMORE study and submitted the data in this supplement. The study supported the safety of uveitis treatment in pediatric patients above the age of 2 years. The uveitis disease course and effect of treatment is considered to be the same in adults and pediatric patients with uveitis. The efficacy demonstrated in the studies of adults is considered supportive of the treatment of uveitis in pediatric patients.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
An OSI investigation was not deemed necessary for this study which was used as partial support of safety.

Financial Disclosures
Abbvie has adequately disclosed financial arrangements with the clinical investigators who participated in the development program for adalimumab. A review of these arrangements do not raise questions about the integrity of the results.

Office of Biostatistics
From the Office of Biostatistics review finalized 8/32018:

The primary endpoint was 'time to treatment failure.' The treatment failure was defined as meeting at least one of the following criteria: worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, nonpermitted use of concomitant medications, and suspension of treatment for an extended period of time.

The SYCAMORE study demonstrated that Adalimumab significantly delayed the time to treatment failure, as compared to placebo ($p < 0.0001$ from log-rank test). See Figure 1 page 3 of this Division Director/ CDTL review. The median time to treatment failure was 24.1 weeks for subjects treated with placebo and was not estimable for subjects treated with adalimumab because fewer than one-half of these subjects experienced treatment failure. Adalimumab statistically significantly reduced the risk of treatment failure by 75% relative to placebo (hazard ration (HR) = 0.25 [95% CI: 0.12, 0.49]; $p < 0.0001$).

12. Labeling

BLA 125057/S-397 Humira (adalimumab) will be approved for the treatment of non-infectious intermediate, posterior and panuveitis in pediatric patients 2 years of age and older with the labeling attached in this review.

13. Postmarketing Recommendations

There is currently a Medication Guide approved for adalimumab. No changes have been made to the Medication Guide exception for the inclusion of a lower age limit for the treatment of uveitis. There are no new Postmarketing Risk Evaluation and Management Strategies recommended. There are no new Postmarketing Requirements and Commitments recommended based on the approval of this supplement.

104 Pages of Draft Labeling have been Withheld in Full immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
09/28/2018

WILEY A CHAMBERS
09/28/2018