Drug Monograph

Drug Name: **Saphnelo™ (anifrolumab-fnia) vial**
Drug Class: **Immunologic Agents: Targeted Immune Modulators, Select Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Saphnelo is available in a single-dose vial containing 300 mg/2 ml of anifrolumab-fnia solution for injection.
Manufacturer:	Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850.
Summary of Findings:	The safety and efficacy of Saphnelo was established by data combined from three randomized, double-blind, placebo-controlled trials (TULIP-1, TULIP-2, and MUSE). Patients in these studies were ≥18 years of age with moderate to severe systemic lupus erythematosus (SLE) receiving standard therapy. Saphnelo's efficacy was based on the assessment of clinical response using the composite endpoints, British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) and SLE Responder Index (SRI-4). The primary endpoint in TULIP-1 was a combined assessment of SRI-4 and sustained reduction in oral corticosteroids (OCS) measured at Week 24 and was met with statistically significant results (p=0.014 for 300 mg dose and p=0.063 for 1000 mg dose).The primary endpoint in Trial 2 was the improvement in disease activity at 52 weeks measured by SRI-4 which did not result in statistically significant results. The endpoint in Trial 3 also looked at disease improvement at 52 weeks but utilized the BICLA for measuring results and the endpoint was met (p=0.001). Combined data found adverse reactions were reported in 87% of patients receiving Saphnelo and in 79% of patients getting placebo. The most common adverse reactions were: upper respiratory infection (435), bronchitis (11%), infusion-related reactions (9.4%), herpes zoster (6.1%), and cough (5%).

Status	☐ Clinical Edit	☐ PA Required
Recommendation:	☐ Open Access	☒ PDL
Type of PA	☐ Appropriate Indications	☒ Non-Preferred
Criteria:	☐ No PA Required	☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Lupus is a chronic autoimmune disease that can cause inflammation and pain in any part of the body. It most commonly affects the skin, joints, and internal organs (e.g., kidneys, heart). Common symptoms are: extreme fatigue; pain or swelling in the joints; swelling in the hands, feet, or around the eyes; headaches; low fevers; sensitivity to sunlight or fluorescent light; chest pain when breathing deeply; butterfly-shaped rash on cheeks and nose; hair loss; sores in mouth or nose; and Raynaud's Disease. There are four kinds of lupus: systemic lupus erythematosus (SLE), cutaneous lupus, drug-induced lupus, and neonatal lupus. Lupus can be challenging to diagnose because the symptoms can mimic many other conditions and the symptoms can come and go or change over time. Diagnosis will be made using a patient's symptoms, lab tests, medical history and family history. Although lab tests alone will not give a definitive diagnosis, the most commonly ordered test called the antinuclear antibody (ANA) test. A positive ANA test will most likely lead to additional testing for further confirmation or elimination of Lupus or other autoimmune conditions. There is no cure for SLE but common treatments for mild symptoms include: hydroxychloroquine or chloroquine, NSAIDs, and short-term use of low-dose glucocorticoids. Patients with moderate symptoms may utilize a small increase in glucocorticoids (taper back down if possible) or a steroid-sparing immunosuppressive agent (e.g., azathioprine, or methotrexate). In order to treat severe symptoms, providers may need to use intensive immunosuppressive therapy, high dose systemic glucocorticoids, or other immunosuppressive agents such as mycophenolate, azathioprine, cyclophosphamide, or rituximab.

Dosage Form [3]

Saphnelo is available in a single-dose vial containing 300 mg/2 ml of anifrolumab-fnia solution for injection.

Manufacturer [3]

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850.

Indication(s) [3]

Saphnelo is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy.

Clinical Efficacy [3,4] (mechanism of action/pharmacology, comparative efficacy)

Saphnelo is a human immunoglobulin G1 kappa ($IgG1_K$) monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR) with high specificity and affinity. This binding inhibits type I IFN signaling, thereby blocking the biologic activity of type I IFNs. Saphnelo also induces the

internalization of IFNAR1, thereby reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor mediated type I IFN signaling inhibits IFN responsive gene expression as well as downstream inflammatory and immunological processes. Inhibition of type I IFNs block plasma cell differentiation and normalizes peripheral T-cell subsets. Type I IFNs play a role in the pathogenesis of SLE. Approximately 60-80% of adult patients with active SLE express elevated levels of type I IFN inducible genes.

Pharmacokinetics:

Absorption	N/A
Metabolism	N/A
Excretion	Systemic clearance (CL): 0.193 L/day
Half-life	N/A

Clinical Trials Experience

STUDY DESIGN	Three, 52-week treatment period, multicenter, randomized, double-blind, placebo-controlled studies (NCT01438489, NCT02446912, and NCT02446899)
INCLUSION CRITERIA	• ≥18 years of age • Moderate to severe disease, with: ○ A SLE Disease Activity Index 2000 (SLEDAI-2K) score of ≥6 points AND ○ Had organ level involvement based on British Isles Lupus Assessment Group (BILAG) assessment AND ○ Physician's Global Assessment (PGA) score ≥1, despite receiving standard SLE therapy consisting of with one or any combination of oral corticosteroids (OCS), antimalarials and/or immunosuppressants at baseline. • Patients continued to receive their existing SLE therapy at stable doses during the trials, with the exception of OCS where tapering was a component of the protocol
EXCLUSION CRITERIA	• Severe active lupus nephritis • Severe active CNS lupus • Use of other biologic agents and cyclophosphamide (required wash out period of at least 5 half-lives prior to enrollment)
TREATMENT REGIMEN	The efficacy of Saphnelo was established based on assessment of clinical response using the composite endpoints, the British Isle Lupus Assessment Group based Composite Lupus Assessment (BICLA) and the SLE Responder Index (SRI-4). BICLE response at Week 52, was defined as improvement in all organ domains with moderate or severe activity at baseline: • Reduction of all baseline BILAG A to B/C/D and baseline BILAG B to C/D, and no worsening in other organ systems,, as defined by ≥1 new BILAG or ≥2 new BILAG B • No worsening from baseline in SLEDAI-2K, where worsening is defined as an increase from baseline of >0 points in SLEDAI-2K • No worsening from baseline in patients' lupus disease activity, where worsening if defined by an increase ≥0.30 points on a 3-point PGA visual analogue scale (VAS) • No discontinuation of treatment • No use of restricted medication beyond the protocol-allowed threshold. SRI-4 response, was defined as meeting each of the following criteria at Week 52 compared with baseline:

- Reduction from baseline of ≥4 points in the SLEDAI-2K
- No new organ system affected as defined by 1 or more BILAG A or 2 or more BILAG B items compared to baseline
- No worsening from baseline in the patients' lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA VAS
- No discontinuation of treatment
- No use of restricted medication beyond the protocol-allowed threshold.

Patients received anifrolumab-fnia or placebo, administered by intravenous infusion, every 4 weeks. Trial 1 randomized 305 patients (1:1:1) who received Saphnelo 300 mg or 1000 mg, or placebo for up to 52 weeks. Trial 2 randomized 457 patients (1:2:2) who received Saphnelo 150 mg, 300 mg or placebo. Trial 3 randomized 362 patients (1:1) who received Saphnelo 300 mg or placebo.

RESULTS

The primary endpoint in Trial 1 was a combined assessment of the SRI-4 and the sustained reduction in OCS (<10 mg/day and ≤OCS dose at week 1, sustained for 12 weeks) measured at Week 24. The primary endpoint in Trial 2 and 3 was the improvement in disease activity evaluated at 52 weeks, measured by SRI-4 in Trial 2 and BICLA in Trial 3. The common secondary endpoints included in Trial 2 and 3 were the maintenance of OCS reduction, improvement in cutaneous SLE activity, and flare rate. During Weeks 8-40, patients with a baseline OCS ≥10 mg/day were required to taper their OCS dose to ≤7.5 mg/day, unless there was worsening of disease activity.

BICLA Response Rate at Week 52

	Trial 1*†		Trial 2*†		Trial 3*‡	
	Saphnelo 300 mg (N=99)	Placebo (N=102)	Saphnelo 300 mg (N=180)	Placebo (N=184)	Saphnelo 300 mg (N=180)	Placebo (N=182)
BICLA Response Rate[ξ]						
Responder n (%)	54 (54.6)	27 (25.8)	85 (47.1)	55 (30.2)	86 (47.8)	57 (31.5)
Difference in Response Rates (95% CI)	28.8 (15.7, 41.9)		17.0 (7.2, 26.8)		16.3 (6.3, 26.3) *p*=0.001	
Components of BICLA Response[ξ]						
BILAG Improvement n (%)	54 (54.5)	28 (27.5)	85 (47.2)	58 (31.5)	88 (48.9)	59 (32.4)
No. of Worsening SEDAI-2K n (%)	73 (73.7)	61 (59.8)	121 (67.2)	104 (56.5)	122 (67.8)	94 (51.6)
No. of Worsening of PGA n (%)	76 (76.8)	62 (60.8)	117 (65.0)	105 (57.1)	122 (67.8)	95 (52.2)

* Not formally tested in a pre-specified testing scheme and findings should be interpreted with caution.
† Based on post hoc analysis
‡ Primary endpoint
ξ In all 3 trials, patients who discontinued investigational product or initiated restricted medications beyond the protocol-specified thresholds are considered non-responders. For consistency, the results presented for Trial 2 represent the post-hoc analysis using restricted medication thresholds as defined in Trial 3.

The reduction in disease activity seen in the BICLA and SRI-4 was related primarily to improvement in the mucocutaneous and musculoskeletal organ systems. The reduction in flare rate in patients receiving Saphnelo compared to patients who received placebo was not statistically significant. In Trial 3, Saphnelo demonstrated statistical significance in improving overall disease activity compared to placebo. In Trials 1 and 2, BICLA was a pre-specified analysis.

SRI-4 Response Rate at Week 52

	Trial 1*		Trial 2†		Trial 3*	
	Saphnelo 300 mg (N=99)	Placebo (N=102)	Saphnelo 300 mg (N=180)	Placebo (N=184)	Saphnelo 300 mg (N=180)	Placebo (N=182)
SRI-4 Response Rateξ						
Responder n (%)	62 (62.8)	41 (38.8)	88 (49.0)	79 (43.0)	100 (55.5)	68 (37.3)
Difference in Response Rates (95% CI)	24.0 (10.9, 37.2)		6.0 (-4.2, 16.2)		18.2 (8.1, 28.3)	
Components of SRI-4 Responseξ						
SLEDAI-2K Improvement n (%)	62 (62.6)	41 (40.2)	89 (49.4)	80 (43.5)	101 (56.1)	71 (39.0)
No. of Worsening BILAG n (%)	75 (75.8)	61 (59.8)	119 (66.1)	105 (57.1)	125 (69.4)	94 (51.6)
No. of Worsening of PGA n (%)	76 (76.8)	62 (60.8)	117 (65.0)	105 (57.1)	122 (67.8)	95 (52.2)

* Not formally tested in a pre-specified testing scheme and findings should be interpreted with caution.
† Primary endpoint
ξ In all 3 trials, patients who discontinued investigational product or initiated restricted medications beyond the protocol-specified thresholds are considered non-responders. For consistency, the results presented for Trial 2 represent the post-hoc analysis using restricted medication thresholds as defined in Trial 3 The most commonly involved SLEDAI-2K organ domains were mucocutaneous, musculoskeletal and immune.

In trial 3, among the 47% of patients with a baseline OCS use ≥10 mg/day, Saphnelo demonstrated a statistically significant difference in the proportion of patients able to reduce OCS use by at least 25% to ≤7.5 mg/day at Week 40 and maintain reduction through Week 52 (p=0.004); 52% (45/87) patients in the Saphnelo group versus 30% (25/83) in the placebo achieved this level of steroid reduction (difference 21% [95% CI: 6.8, 35.7]). Consistent trends in favor of Saphnelo compared to placebo, on effect of reduction of OCS use, were observed in Trial 1 and 2, but the difference was not statistically significant.

SAFETY

Discussed in the Adverse Effects section below.

Contraindications (3,4)

- History of anaphylaxis with Saphnelo or its components

Warnings and Precautions (3,4)

- Serious infections
- Hypersensitivity reactions including anaphylaxis
- Malignancy
- Avoid concurrent use of live or live-attenuated vaccines
- Not recommended for concomitant use with other biologic therapies

Adverse Effects [3,4]

Most common, ≥2%	Saphnelo (N=459) %	Placebo (N=466) %
Upper respiratory tract infection*	34	23
Bronchitis**	11	5.2
Infusion-related reactions	9.4	7.1
Herpes Zoster	6.1	1.3
Cough	5.0	3.2
Respiratory tract infection***	3.3	1.5
Hypersensitivity	2.8	0.6

All patients received standard therapy
*Upper respiratory tract infections (including Upper respiratory tract infections, Nasopharyngitis, Pharyngitis)
**Bronchitis (including Bronchitis, Bronchitis viral, Tracheobronchitis)
***Respiratory tract infection (including Respiratory tract infection, Respiratory tract infection viral, Respiratory tract infection bacterial)

Drug Interactions [3,4]

- No formal drug interaction studies have been conducted.

Dosage and Administration [3,4]

The recommended dosage is 300 mg as an intravenous infusion over a 30-minute period every 4 weeks. If a planned infusion is missed, administer Saphnelo as soon as possible. Maintain a minimum interval of 14 days between infusions.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Anifrolumab-fnia	Saphnelo™	AstraZeneca	300 mg IV every 4 weeks	$4,600.54
Belimumab	Benlysta®	Human Genome Sciences/GSK	10mg/kg/dose IV every 2 weeks for first 3 doses, then every 4 weeks thereafter **OR** 200 mg subcutaneously once weekly	$3,720 (IV, for 70 kg patient) **OR** $3,983.12 (SC)

** Wholesale Acquisition Cost

Conclusion

Lupus is a chronic autoimmune disease that can cause inflammation and pain in any part of the body. It most commonly affects the skin, joints, and internal organs (e.g., kidneys, heart). The approval of Saphnelo is the first for a type I interferon receptor antagonist and is the first new option for SLE since 2011. Clinical trials differed in the instrument used to assess disease improvement and showed mixed results with Trial 1 and 3 meeting the primary endpoint but Trial 2 did not meet the primary endpoint. Saphnelo may be better able to compete in the immune modulators for lupus market once AstraZeneca releases the subcutaneous formulation currently in development and gets expanded approval from the FDA for lupus nephritis.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) Lupus Foundation of America [website]. Available at: https://www.lupus.org. Accessed October 25, 2021.
2) Lupus General Overview [Clinical Snapshot]. Available at: https:secure.ipdanalytics. Accessed October 25, 2021.
3) Saphnelo™ (anifrolumab) [Package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2021.
4) IPD Analytics: New Drug Review: Saphnelo (anifrolumab). Accessed October 1, 2021.

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