LUPKYNIS (voclosporin)

The US Food and Drug Administration approved Lupkynis on January 22, 2021 with the following Indications and Usage and Important Safety Information:

LUPKYNIS is indicated in combination with a background immunosuppressive therapy regimen *[see Clinical Studies (14)]* for the treatment of adult patients with active lupus nephritis (LN).

Limitations of Use: Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

IMPORTANT SAFETY INFORMATION

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing malignancies and serious infections with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death.

CONTRAINDICATIONS: LUPKYNIS is contraindicated in patients taking strong CYP3A4 inhibitors because of the increased risk of acute and/or chronic nephrotoxicity, and in patients who have had a serious/severe hypersensitivity reaction to LUPKYNIS or its excipients.

Disease Overview

Systemic lupus erythematosus (SLE) is an autoimmune disease that may affect almost every organ in the body. Renal involvement, LN, occurs in approximately 40% of patients with SLE and causes damage and scarring of the kidneys that may eventually result in kidney failure. Approximately 10% to 30% of patients with LN progress to kidney failure ≤15 years after diagnosis. Patients with LN have ~2x higher rates of hospitalization, ~2x longer hospital stays, and ~5x greater annual healthcare costs if kidney failure develops compared to SLE. Protein in the urine (proteinuria) has been shown to be a strong indicator of LN activity and progression. An increasingly large body of evidence suggests that following initiation of treatment, early improvement in proteinuria (i.e., ≤0.5 mg/mg) is associated with good long-term renal outcomes, however, only ~50% of patients receiving the current standard of care attain a clinically meaningful response in proteinuria, defined as at least a 50% reduction in proteinuria after one year of treatment.

The key components of traditional standard of care (SOC) for LN are immunosuppressants (mycophenolate mofetil [MMF] or cyclophosphamide [CY]) plus corticosteroids (CS), but neither are approved for this use by the FDA. In addition to relatively modest efficacy results with these standard regimens in clinical studies, CS are associated with a cumulative risk of adverse events, including potentially serious complications (i.e., osteoporosis, cataracts, organ damage, etc.).

Thus, there is substantial unmet medical need for a treatment that more significantly and more rapidly increases the rates of complete renal response while reducing the reliance on high doses of corticosteroids. Voclosporin is a next generation calcineurin inhibitor immunosuppressant, structurally similar to cyclosporine A, with the addition of a single carbon extension with a double-bond that changes how voclosporin binds to calcineurin. The dual MOA involves both immunosuppression as well as podocyte stabilization within the glomeruli. Voclosporin demonstrates consistent dose-concentration, eliminating the need for therapeutic drug monitoring, as well as increased potency compared with cyclosporine and no drug-drug interaction with MMF. The starting dose of voclosporin is 23.7mg taken orally BID and can easily be adjusted based on the patient's eGFR.

Efficacy and Effectiveness of LUPKYNIS

The efficacy and safety of LUPKYNIS have been evaluated in a comprehensive clinical program, comparing placebo with LUPKYNIS, with all treatment arms receiving background therapy with MMF and strictly-tapered CS

Importantly, both studies shared a common and stringent composite primary endpoint of complete renal response: UPCR ≤0.5 while maintaining renal function (eGFR ≥ 60 ml/), without rescue medications and in the presence of protocol-mandated, low-dose steroids (80% of patients on ≤ 2.5mg/day oral prednisone at week 16).

AURA-LV: In a Phase 2b, placebo-controlled, randomized, double-blind, international, multicenter, 48-week trial (N=265), significantly more patients receiving LUPKYNIS 23.7 mg twice daily (BID) achieved a complete renal response at Week 24 (32.6%) vs. placebo (19.3%), resulting in an odds ratio (OR) of 2.03 (p=0.046).

AURORA 1: In the pivotal Phase 3, placebo-controlled, randomized, double-blind, international, multicenter 52-week trial (N=357), significantly more patients receiving LUPKYNIS 23.7mg BID + SOC vs. placebo + SOC achieved the primary endpoint of complete renal response at Week 52: 40.8% vs. 22.5% (p<0.001; OR of 2.7). Significant improvements were also seen in all key secondary endpoints including renal response at 24 weeks (32% vs. 20%, p=0.002), partial renal response at 24 weeks (70% vs. 50%, p<0.001), partial renal response at 52 weeks (70% vs. 52%, p<0.001) and median time to 50% reduction in urine protein creatinine ratio (UPCR) (29 days vs. 63 days, p<0.001) compared to placebo. Importantly, the median time to UPCR of ≤0.5 mg/mg was shorter in the LUPKYNIS arm than the placebo arm (169 days vs. 372 days). In addition, approximately 80% of subjects in both treatment arms had successfully reduced their steroid dose to ≤2.5mg by the Week 16 visit, as per the protocol steroid tapering guidance. Around three quarters of subjects who completed the study were taking ≤2.5 mg oral CS at Week 52.

Safety and Tolerability of LUPKYNIS

An integrated analysis was conducted of safety data for the AURA-LV and AURORA-1 for up to 1 year of exposure to LUPKYNIS. A total of 355 patients with LN were treated with voclosporin in the Phase 2b and 3 clinical studies with 224 exposed for at least 48 weeks.

The most commonly reported adverse reactions (≥3%) were glomerular filtration rate decrease, hypertension, diarrhea, headache, anemia, cough, urinary tract infection, abdominal pain upper, dyspepsia, alopecia, renal impairment, abdominal pain, mouth ulceration, fatigue, tremor, acute kidney injury, and decreased appetite.

Glomerular filtration rate decrease was the most frequently reported adverse reaction, reported in placebo (11.3 per 100 patient-years), LUPKYNIS 23.7 mg (37.1 per 100 patient-years), and voclosporin 39.5 mg BID (48.7 per 100 patient-years). With LUPKYNIS 23.7 mg BID, decreases in glomerular filtration rate occurred within the first 3 months in 71% of patients, with 78% of those resolved or improved following dose modification, and of those 64% resolved or improved within 1 month. Decreases in glomerular filtration rate resulted in permanent discontinuation of LUPKYNIS in 14% of patients and resolved in 40% within 3 months after treatment discontinuation.

Conclusions

LN is a serious and complex disease that results in a high humanistic and economic burden to both patients and the healthcare system. Proteinuria is the best indicator of disease activity and progression. The goal of therapy is to achieve low levels of proteinuria early, which is associated with better long-term outcomes. The combination of LUPKYNIS with the traditional standard of care results in higher rates of complete renal response in shorter periods of time, compared to standard of care alone. In addition, the majority of patients who achieved complete renal response did so while on low doses of corticosteroids. Thus, LUPKYNIS, the first FDA-approved oral treatment for LN, provides an effective and safe treatment option for LN patients with a modest impact on health plan formularies and a number needed to treat (NNT) of 5.5. Lastly, The Institute for Clinical and Economic Review (ICER) has stated that evidence supports improved clinical outcomes for patients and may offer important benefits beyond those directly measured in clinical and cost-effectiveness analyses.