NEW DRUG APPROVAL

Brand Name	Tarpeyo™
Generic Name	budesonide
Drug Manufacturer	Calliditas Therapeutics AB

New Drug Approval

FDA Approval Date: December 15, 2021

Review Designation: Priority; Orphan

Type of Review: Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 215935

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

IgA nephropathy, also known as Berger's disease, is a rare kidney disease that occurs when IgA (a type of antibody) deposits build up in the kidneys, causing inflammation that damages kidney tissues. The deposits can cause the kidneys to leak blood and protein into the urine. IgA nephropathy complications can include high blood pressure and chronic kidney disease, which can sometimes progress to kidney failure.

IgAN is the most common lesion found to cause primary glomerulonephritis throughout most resource-abundant countries of the world. IgAN occurs with greatest frequency in East Asian individuals and White individuals and is relatively rare in Black individuals. In a Chinese study of 13,519 kidney biopsies, for example, IgAN constituted 45 percent of all cases of primary glomerulonephritis.

Variations in disease prevalence may reflect regional differences in screening for kidney disease and kidney biopsy practices. IgAN can only be diagnosed upon evaluation of a kidney biopsy with immunofluorescence microscopy. Thus, the incidence and prevalence of IgAN will be higher in places where kidney biopsies are performed more frequently. Many patients with IgAN are detected on routine urine screening because their only clinical manifestation is asymptomatic hematuria and/or proteinuria. Prevalence may therefore appear to be higher in countries with an active urine testing program and a low threshold for the performance of kidney biopsy in patients with isolated asymptomatic hematuria, such as Japan and Korea, where testing is routinely performed in schools and in the workplace. Conversely, clinicians in North America seldom biopsy a patient with isolated hematuria or mild proteinuria, resulting in an apparently lower disease prevalence.

Patients with IgAN may present at any age, but there is a peak incidence in the second and third decades of life. There is approximately a 2:1 male-to-female predominance in North American and Western European populations, although the sexes are equally affected among populations in East Asia. Significant heterogeneity in clinical presentation and pathological features also exists between geographical locations, which may in part explain differences in response to immunomodulatory therapies.

Efficacy

Treatment of IgAN:

The effect of Tarpeyo™ on proteinuria was assessed in a randomized, double-blind, multicenter study (Nef301, NCT: 03643965) in patients with biopsy-proven IgAN, eGFR ≥35 mL/min/1.73 m2, and proteinuria (defined as either ≥1 g/day or UPCR ≥0.8 g/g) who were on a stable dose of maximally tolerated RAS inhibitor therapy. Patients with other glomerulopathies, nephrotic syndrome, or those who had been treated with systemic

immunosuppressive medications were excluded. Patients were randomized 1:1 to either Tarpeyo™ 16 mg once daily or placebo and treated for nine months followed by a 2-week taper of either Tarpeyo™ 8 mg once daily or placebo.
Of the 199 patients who completed the Month 9 visit, 68% were male, 86% were Caucasian, 12% were Asian, and 16% were from the US. The median age was 44 years (range 23 to 73 years). At baseline, the mean eGFR was approximately 58 mL/min/1.73 m2, with 62% of patients having an eGFR 3.5 g/24 hours. Approximately 73% of patients had a history of hypertension and 5% had a history of type 2 diabetes mellitus. At baseline, 98% were treated with an ACE inhibitor or ARB and < 1% of patients were on an SGLT2 inhibitor.
The primary endpoint was the percentage reduction in UPCR at 9 months compared to baseline.

Table- Analysis of the primary efficacy endpoint at 9 months in Phase 3 Study Nef-301

Primary Endpoint: UPCR g/g [a]	**TARPEYO 16 mg (N=97)**	**Placebo (N=102)**
Percentage reduction from baseline (Adjusted for baseline) [b]	34%	5%
TARPEYO 16 mg versus Placebo : Percentage reduction (95% CI) [c]; 2-sided p-value	31% (16% to 42%); p=0.0001	

[a] All patients with a UPCR reading regardless of use of prohibited medication at 9 months.
[b] Adjusted geometric least squares mean ratio of UPCR relative to baseline were based on a longitudinal repeated measures model.
[c] The estimate of the ratio of geometric mean ratio of UPCR relative to baseline comparing TARPEYO 16 mg with placebo was reported as percentage reduction along with the respective 95% confidence interval from the longitudinal repeated measures model and p-values.
CI: confidence interval; UPCR: urine protein creatinine ratio.

The treatment effect for the UPCR endpoint at 9 months were consistent across key subgroups, including key demographic (such as age, sex, race) and baseline disease (such as baseline proteinuria) characteristics.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥5%) are hypertension, peripheral edema, muscle spasms, acne, dermatitis, weight increase, dyspnea, face edema, dyspepsia, fatigue, hirsutism.

WARNINGS & PRECAUTIONS

- Hypercorticism and Adrenal Axis Suppression: Follow general warnings concerning corticosteroids, patients with hepatic impairment may be at increased risk. Taper upon discontinuation.
- Risks of immunosuppression: Avoid use in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. May affect vaccine efficacy.
- Other Corticosteroid Effects: Monitor patients with concomitant conditions where corticosteroids may have unwanted effects (e.g., hypertension, diabetes mellitus).

CONTRAINDICATIONS

- Hypersensitivity to budesonide or any of the ingredients in Tarpeyo™.

Clinical Pharmacology

MECHANISMS OF ACTION

Budesonide is a corticosteroid with potent glucocorticoid activity and weak mineralocorticoid activity that undergoes substantial first pass metabolism. Mucosal B-cells present in the ileum, including the Peyer's patches,

express glucocorticoid receptors and are responsible for the production of galactose-deficient IgA1 antibodies (Gd-Ag1) causing IgA nephropathy. Through their anti-inflammatory and immunosuppressive effects at the glucocorticoid receptor, corticosteroids can modulate B-cell numbers and activity. It has not been established to what extent Tarpeyo™ efficacy is mediated via local effects in the ileum vs systemic effects.

Dose & Administration

ADULTS

16 mg orally once daily in the morning. Recommended therapy duration is 9 months. When discontinuing therapy, reduce the dosage to 8 mg orally once daily for the last 2 weeks of therapy.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment required.

HEPATIC IMPAIRMENT

No dosage adjustment required.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Delayed release capsules: 4 mg.