budesonide (Tarpeyo™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO258

Description

Budesonide (Tarpeyo) is an orally administered corticosteroid indicated to reduce the loss of kidney function in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression.

Length of Authorization

- Initial: Ten months
- Renewal: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
budesonide (Tarpeyo)	Primary Immunoglobulin A Nephropathy (IgAN)	4 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Budesonide (Tarpeyo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a nephrologist; **AND**
   C. A diagnosis of **primary immunoglobulin A nephropathy (IgAN)** when the following are met:
      1. Diagnosis of Primary immunoglobulin A nephropathy (IgAN) has been confirmed by a kidney biopsy; **AND**
      2. Member has an eGFR ≥ 35mL/min/1.73 m^2; **AND**
      3. Documentation of elevated protein levels in urine as indicated by proteinuria ≥ 1 g/day or urine protein to creatinine ratio (UPCR) of ≥ 1.5 g/g; **AND**
      4. Member has been optimized on an ACE inhibitor (e.g., lisinopril, benazepril, etc.) or an ARB (e.g., losartan, olmesartan, valsartan, etc.) at a maximum tolerated dose for at least three months; **AND**
      5. Treatment will be used in combination with an ACE inhibitor or ARB; **OR**
         i. Treatment with an ACE inhibitor or ARB has been contraindicated or not tolerated; **AND**
      6. Member has documentation of intolerance or contraindication to generic systemic corticosteroid therapy (e.g., prednisone, prednisolone, methylprednisolone).

II. Budesonide (Tarpeyo) is considered investigational when used for all other conditions, including but not limited to:
   A. IgAN in members less than 18 years of age
   B. Secondary IgA Nephropathy
   C. Budesonide (Tarpeyo) used in combination with sparsentan (Filspari)
   D. Focal segmental glomerulosclerosis (FSGS)
   E. Chronic kidney disease (CKD) other than primary IgAN

Renewal Evaluation

I. N/A – Product not eligible for renewal

Supporting Evidence

I. Budesonide (Tarpeyo) is the first therapy FDA approved for the treatment of patients with primary immunoglobulin A (IgA) nephropathy. IgA nephropathy, also known as Berger's disease, is a rare kidney disease that occurs when IgA 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. As such, patients should be managed in consultation with a nephrologist.

II. Clinical studies NEFIGAN and NefIgArd were conducted in adult patient populations (18 years of age and older). The efficacy and safety of budesonide (Tarpeyo) in pediatric populations is unknown at this time. Additionally, guidelines indicate there is insufficient data currently available to recommend that pediatric IgAN populations be managed as adults.

III. Budesonide (Tarpeyo) was studied in a phase 3, multicenter, randomized, double-blind, placebo controlled trial (NefIgArd). The trial consisted of two parts. Part A which included a screening period, 9-month treatment period, with a 3-month follow-up (including a 2-week taper) and part B which consisted of a 15-month observational follow-up period where no treatment was given. The primary endpoint of part A was the ratio of urinary protein-creatinine ratio (UPCR) at 9 months following the first dose of study drug compared to baseline. In part B, the primary endpoint assessed the time-weighted average of change in eGFR from baseline.
   - The trial met the prespecified part A primary endpoint based on an interim analysis of 199 randomized patients who had completed the Month 9 visit. The interim analysis showed a 31% reduction in UPCR in patients treated with budesonide (Tarpeyo) 16 mg once daily compared to placebo (95% CI: 16% to 42% reduction; p=0.0001). In the final analysis of 364 patients, the percentage change in UPCR observed at 9 months was consistent with the results in the subset of 199 patients included in the interim analysis.

- In the final analysis of 364 patients, the trial met the prespecified part B primary endpoint (p<0.0001). The favorable effect of budesonide (Tarpeyo) on eGFR was seen by Month 3 (the earliest assessment) and did not appear to increase in magnitude over two years. At Year 2, there was a 5.9 mL/min/1.73 m2 difference in the mean change from baseline in eGFR between budesonide (Tarpeyo) and placebo (95% CI: 3.3 to 8.5 mL/min/1.73 m2 ; p<0.0001).
- The most commonly reported treatment-emergent adverse events during treatment with budesonide (Tarpeyo) were peripheral edema (31 [17%] of 182 patients vs placebo, 7 [4%] of 182 patients), hypertension (22 [12%] vs six [3%]), muscle spasms (22 [12%] vs 7 [4%] patients), acne (20 [11%] vs 2 [1%]), and headache (19 [10%] vs 14 [8%]).

IV. In clinical studies participants underwent treatment for budesonide (Tarpeyo) for nine months followed by a two-week dose taper. Given treatment is a course of high dose steroid, dose tapering is recommended to avoid steroid withdrawal syndrome.

V. KDIGO guidelines indicate IgAN can only be diagnosed with a kidney biopsy. While there are several prognostic scoring tools that have been developed to assist in predicting kidney outcomes of IgAN patients (i.e., MEST-C, International IgAN Prediction Tool, etc.) there are currently are no validated diagnostic serum or urine biomarkers.

VI. Reduced glomerular filtration rates can be a marker of kidney disease; specifically, those under 35mL/min/1.73 m^2 which can indicate moderate-to-severe kidney disease (stage 3b). Guidelines recommend supportive care for these patients with moderate-to-severe kidney disease as opposed to therapy with corticosteroids.

VII. The primary focus of IgAN management is optimized supportive care (i.e., blood pressure management, maximally tolerated ACEi/ARBs, lifestyle modification, and reduction of cardiovascular risks). Proteinuria and eGFR are the only validated prognostic serum or urine biomarkers in IgAN. In all types of proteinuric glomerular diseases, including IgAN, higher levels of proteinuria are associated with worse kidney outcomes (acute kidney injury, chronic kidney disease, end stage renal disease, etc.). Reduction in proteinuria, independent of blood pressure control, is associated with improved kidney outcomes. KDIGO guidelines recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB to further protect renal function.

VIII. Patients with IgAN who are at high risk of progressive chronic kidney disease (CKD) despite maximal supportive care are defined as those with proteinuria greater than 0.75 to 1 g/day despite treatment with a maximally tolerated or allowed daily dose of RAS blockade (ACEi/ARB) for ≥ 3 months. Guideline recommendations indicate proteinuria reduction to under 1 g/day as a surrogate marker of improved kidney outcomes in IgAN. Furthermore, a reduction to under 1 g/day is a reasonable treatment target.

IX. Incremental levels of sustained proteinuria above 1 g/d are associated with marked changes in the risk of loss of kidney function. Reduction of proteinuria, ideally to under 1 g/d, is associated

with favorable outcomes. The urinary protein-creatinine ratio (UPCR) has relatively poor correlation with 24-hour urine protein excretion, particularly when proteinuria is over 1 g/d. This makes distinguishing smaller changes in proteinuria (e.g., 1.5 vs 2 g/d) challenging. UPCR cannot be directly compared with a 24-h proteinuria level; however, UPCR gives the ability to overcome possible collection errors and deviations from normal creatinine excretion (e.g., physically active and muscular men). Due to this reason both can be used to assess proteinuria.

X. Budesonide (Tarpeyo) has not been included in KDIGO guidelines. Currently guidelines recommend enrollment into clinical trials prior to use of corticosteroids or other immunosuppressants. If the benefit outweighs the risk, treatment with prednisone or methylprednisolone is recommended based on limited clinical trial experience. Budesonide (Tarpeyo) was able to show sustained benefit UPCR reduction eGFR maintenance at two years. Other glucocorticoid therapies (prednisone, methylprednisolone, and IV methylprednisolone) have demonstrated similar reductions in proteinuria and have comparable safety profiles to budesonide (Tarpeyo). It is unknown if budesonide (Tarpeyo) is superior to other glucocorticoid therapies that could be utilized. Additionally, budesonide (Tarpeyo) is significantly more costly than other glucocorticoid therapies. Of the other alternative agents, mycophenolate Mofetil (MMF) is the preferred option. There is limited clinical data to support the use of other immunosuppressive agents.

XI. Endpoints from other corticosteroid studies followed patients for up to 10 years. Safety and efficacy of treatment with subsequent courses of budesonide (Tarpeyo) have not been established at this time. Data to support possible retreatment with budesonide (Tarpeyo) is under evaluation in the NefigArd-OLE trial program. Similarly designed trials with long-term safety data have limited total glucocorticoid exposure to six months due to increased risks of treatment-related adverse events (infection risk, impaired glucose tolerance, weight gain, etc.).

Investigational or Not Medically Necessary Uses

I. Budesonide (Tarpeyo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. IgAN in members less than 18 years of age
      i. The use of budesonide (Tarpeyo) has not been evaluated in children. Additionally, while guidelines acknowledge use of immunosuppressants, specifically corticosteroids, are more widespread in children there is a lack of randomized controlled trials and consensus-driven indications for use in pediatric populations. As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.
   B. Secondary IgA Nephropathy

i. Secondary IgAN can be attributed to a variety of other disorders including but not limited to cirrhosis and other severe forms of liver disease, celiac disease, HIV infection, monoclonal gammopathy of renal significance (MGRS), seronegative arthritis, etc. While there is no standard of care treatment for IgAN in these patients, therapy should be directed at the underlying primary disease.

C. Budesonide (Tarpeyo) used in combination with Sparsentan (Filspari)
D. Focal segmental glomerulosclerosis (FSGS)
E. Chronic kidney disease (CKD) other than primary IgAN

References

1. Tarpeyo [Prescribing Information]. Stockholm, Sweden: Calliditas Therapeutics AB. December 2023.
2. Lafayette R, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial [published correction appears in *Lancet*. 2023 Sep 9;402(10405):850]. Lancet. 2023;402(10405):859-870.
3. Fellström BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet*. 2017;389(10084):2117-2127. doi:10.1016/S0140-6736(17)30550-0
4. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021
5. UpToDate, Inc. IgA nephropathy: Clinical features and diagnosis. UpToDate [database online]. Waltham, MA. Last updated February 9, 2022. Available at: http://www.uptodate.com/home/index.html.
6. UpToDate, Inc. IgA nephropathy: Treatment and prognosis. UpToDate [database online]. Waltham, MA. Last updated January 3, 2022. Available at: http://www.uptodate.com/home/index.html.
7. Pattrapornpisut, P., Avila-Casado, C., & Reich, H. N. (2021). Iga nephropathy: Core curriculum 2021. American Journal of Kidney Diseases, 78(3), 429–441. https://doi.org/10.1053/j.ajkd.2021.01.024

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease State
sparsentan (Filspari)	Primary IgA nephropathy; at high risk of progression

Policy Implementation/Update:

Action and Summary of Changes	Date
Added related policies table. Updated to allow a pathway to coverage through standard criteria.	01/2023
Policy created.	04/2022