

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215935Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TARPEYO safely and effectively. See full prescribing information for TARPEYO.

TARPEYO (budesonide) delayed release capsules, for oral use
Initial U.S. Approval: 1997

INDICATIONS AND USAGE

TARPEYO is a corticosteroid indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g. (1)

This indication is approved under accelerated approval based on a reduction in proteinuria. It has not been established whether TARPEYO slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 16 mg administered orally once daily, in the morning at least 1 hour before a meal. (2)
- Swallow whole. Do not open, crush or chew. (2)
When discontinuing, reduce dosage to 8 mg once daily for the last two weeks. (2, 5.1)

DOSAGE FORMS AND STRENGTHS

Delayed release capsules: 4 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to budesonide or any of the ingredients in TARPEYO. (4)

WARNINGS AND PRECAUTIONS

- Hypercorticism and Adrenal Axis Suppression:** Follow general warnings concerning corticosteroids, patients with hepatic impairment may be at increased risk. Taper upon discontinuation. (2, 5.1, 8.6, 12.3)
- 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. (5.2)
- Other Corticosteroid Effects:** Monitor patients with concomitant conditions where corticosteroids may have unwanted effects (e.g., hypertension, diabetes mellitus). (5.3)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$) are hypertension, peripheral edema, muscle spasms, acne, dermatitis, weight increase, dyspnea, face edema, dyspepsia, fatigue, hirsutism. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Calliditas Therapeutics at 1-844-IGA-0011 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Potent CYP3A4 Inhibitors (e.g. ketoconazole, grapefruit juice): Can increase systemic budesonide concentrations: avoid concomitant use. (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Routine monitoring of linear growth in infants is recommended with chronic use of budesonide in the nursing mother. (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hypercorticism and Adrenal Axis Suppression
- 5.2 Risks of Immunosuppression
- 5.3 Other Corticosteroid Effects

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Interaction with CYP3A4 Inhibitors

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Treatment of IgAN

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TARPEYO is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g.

This indication is approved under accelerated approval based on a reduction in proteinuria. It has not been established whether TARPEYO slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

2 DOSAGE AND ADMINISTRATION

The recommended duration of therapy is 9 months, with a dosage of 16 mg administered orally once daily [see *Clinical Studies (14.1)*]. When discontinuing therapy, reduce the dosage to 8 mg once daily for the last 2 weeks of therapy [see *Warnings and Precautions (5.1)*].

The delayed release capsules should be swallowed whole in the morning, at least 1 hour before a meal. Do not open, crush or chew.

If a dose is missed, take the prescribed dose at the next scheduled time. Do not double the next dose.

Safety and efficacy of treatment with subsequent courses of TARPEYO have not been established.

3 DOSAGE FORMS AND STRENGTHS

Delayed release capsule containing 4 mg budesonide. White coated opaque capsules printed with “CAL10 4MG” in black ink.

4 CONTRAINDICATIONS

TARPEYO is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of TARPEYO. Serious hypersensitivity reactions, including anaphylaxis have occurred with other budesonide formulations.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Axis Suppression

When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy [see *Dosing and Administration (2)*] or switching between corticosteroids, monitor for signs of adrenal axis suppression.

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased

signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B) [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

5.2 Risks of Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. Avoid exposure to active, easily-transmitted infections (e.g., chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.

How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, consider therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG). If exposed to measles, consider prophylaxis with pooled intramuscular immunoglobulin (IG). If chickenpox develops, consider treatment with antiviral agents.

5.3 Other Corticosteroid Effects

TARPEYO is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where corticosteroids may have unwanted effects.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypercorticism and adrenal suppression [see Warnings and Precautions (5.1)]
- Risks of immunosuppression [see Warnings and Precautions (5.2)]
- Other corticosteroid effects [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TARPEYO has been evaluated in a randomized controlled study in 197 patients.

The most common adverse reactions reported in greater than or equal to 5% of TARPEYO-treated patients are listed in Table 1.

The majority of adverse reactions were mild or moderate in severity.

Table 1: Reported adverse reactions occurring in greater than or equal to 5% of TARPEYO treated patients, and greater than or equal to 2% higher than Placebo

Adverse Reaction	TARPEYO 16 mg (N=97)	Placebo (N=100)
------------------	-------------------------	--------------------

	n (%)	n (%)
Patients with any Adverse Reaction	84 (87)	73 (73)
Hypertension	15 (16)	2 (2)
Peripheral edema	14 (14)	4 (4)
Muscle spasms	13 (13)	4 (4)
Acne	11 (11)	2 (2)
Dermatitis	7 (7)	1 (1)
Weight increased	7 (7)	3 (3)
Dyspnea	6 (6)	0 (0)
Face edema	6 (6)	1 (1)
Dyspepsia	5 (5)	2 (2)
Fatigue	5 (5)	2 (2)
Hirsutism	5 (5)	0 (0)

Most adverse reactions that occurred at a greater incidence for TARPEYO compared to placebo were consistent with hypercortisolism.

7 DRUG INTERACTIONS

7.1 Interaction with CYP3A4 Inhibitors

Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors; e.g. ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine [*see Clinical Pharmacology (12.3)*].

Avoid ingestion of grapefruit juice with TARPEYO. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data from published case series, epidemiological studies and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgA Nephropathy. Infants exposed to in-utero corticosteroids, including budesonide, are at risk for hypoadrenalism (*see Clinical Considerations*). In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.3 times or 0.03 times, respectively, the maximum recommended human dose (MRHD), resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels (*see Data*).

The estimated background risk of major birth defects and miscarriage of the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

IgA nephropathy in pregnancy is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight.

Fetal/Neonatal Adverse Reactions

Hypoadrenalism may occur in infants born to mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly [see *Warnings and Precautions* (5.1)].

Data

Animal Data

Budesonide was teratogenic and embryo-lethal in rabbits and rats.

In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis on gestation days 6 to 15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose (MRHD) on a body surface area basis).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis on gestation days 6 to 18, there was an increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses from approximately 25 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis).

Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.006 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose on a body surface area basis).

In a peri- and post-natal development study, subcutaneous treatment of pregnant rats with budesonide during the period from Day 15 post coitum to Day 21 post partum, budesonide had no effects on delivery, but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures ≥ 0.012 times the MRHD (on a mg/m² basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

8.2 Lactation

Risk Summary

Breastfeeding is not expected to result in significant exposure of the infant to TARPEYO. Lactation studies have not been conducted with oral budesonide, including TARPEYO, and no information is available on the effects of the drug on the breastfed infant or the effects on the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide (*see Data*). Routine monitoring of linear growth in infants is recommended with chronic use of budesonide in the nursing mother. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TARPEYO and any potential adverse effects on the breastfed infant from TARPEYO, or from the underlying maternal condition.

Data

One published study reports that budesonide is present in human milk following maternal inhalation of budesonide, which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk to plasma ratio was approximately 0.5. Budesonide was not detected in plasma, and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide.

Assuming a daily average milk intake of about 150 mL/kg/day and a milk to plasma ratio of 0.5, the estimated oral dose of budesonide for a 5 kg infant is expected to be less than 2 mcg/day for a maternal dose of 16 mg TARPEYO. Assuming 100% bio-availability in the infant this is about 0.1% of the maternal dose and about 3% of the highest inhaled dose used clinically for asthma in infants.

8.4 Pediatric Use

The safety and efficacy of TARPEYO in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of TARPEYO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to budesonide [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*]. Avoid use in patients with severe hepatic impairments (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

10 OVERDOSAGE

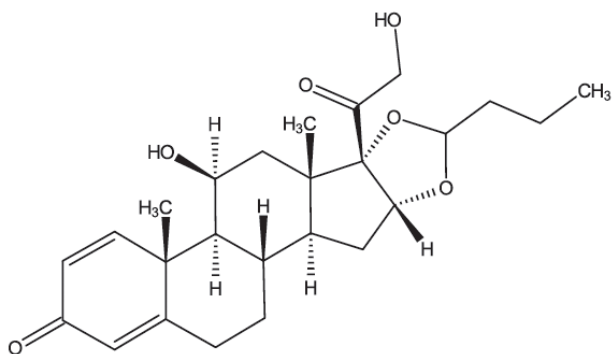
Reports of acute toxicity and/or death following overdosage of corticoids are rare.

In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy.

11 DESCRIPTION

TARPEYO (budesonide) delayed release capsules, for oral administration, contain budesonide, a synthetic corticosteroid, as the active ingredient. Budesonide is designated chemically as 16 α , 17 α -[(1RS)-Butylidenebis(oxy)]-11 β , 21-dihydroxypregna-1,4-diene-3,20-dione.

Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water, sparingly soluble in alcohol, and freely soluble in chloroform.

The beads in each capsule contain the following inactive ingredients: sugar spheres (sucrose and starch), hypromellose, polyethylene glycol, citric acid monohydrate, ethyl cellulose, medium chain triglycerides and oleic acid. The capsule shells contain hypromellose and titanium oxide (E171); and the printing ink on the capsules contain shellac, propylene glycol and black iron oxide (E172). The enteric coating on the capsules contain: methacrylic acid and methacrylate copolymer, talc and dibutyl sebacate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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's efficacy is mediated via local effects in the ileum vs systemic effects.

12.2 Pharmacodynamics

Treatment with corticosteroids, including TARPEYO, is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function.

12.3 Pharmacokinetics

Absorption

Following single oral administration of TARPEYO 16 mg to healthy subjects, the average geometric mean C_{max} (CV%) was 4.4 ng/mL (58.3), and AUC_{0-24} was 24.1 h*ng/mL (49.7). Median T_{lag} (min, max) was 3.1 h (0, 6) while median T_{max} (min, max) was 5.1 h (4.5, 10).

Food Effect

There was no clinically relevant food effect observed on the overall systemic exposure of budesonide when either a moderate or high fat meal was consumed 1 hour after administration of TARPEYO.

Distribution

Approximately 85 to 90% of budesonide binds to plasma proteins in blood over the concentration range of 0.43 to 99 ng/mL. The volume of distribution at steady state reported in the literature is 3 to 4 L/kg.

Metabolism

Budesonide is metabolized by the liver (and to lesser extent the gut), primarily by oxidative pathways via CYP3A4 to two main metabolites, 16 α -hydroxyprednisolone and 6 β -hydroxybudesonide, which have less than 1% of the corticosteroid activity of budesonide.

Elimination

Budesonide had a high plasma clearance, 0.9 to 1.8 L/min in healthy adults, which is close to the estimated liver blood flow, and, accordingly, suggests that budesonide is a high hepatic clearance drug.

Following single oral administration of TARPEYO 16 mg to healthy subjects, the elimination half-life ($t_{1/2}$) for TARPEYO ranged from 5.0 to 6.8 hours.

Excretion

Budesonide was excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [^3H]-budesonide, approximately 60% of the recovered radioactivity was found in urine. The major metabolites, including 16 α -hydroxyprednisolone and 6 β -hydroxybudesonide, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide was detected in urine.

Specific Populations

Age, race, and body weight

The effect of age, race, and body weight on the pharmacokinetics of TARPEYO has not been established.

Sex

Of the 143 healthy volunteers included in the Phase 1 studies, 29% were female. Pharmacokinetics of budesonide was similar between males and females.

Hepatic Impairment

Subjects with moderate hepatic impairment (Child-Pugh class B) had 3.5 times the budesonide AUC compared with healthy volunteers while subjects with mild hepatic impairment (Child-Pugh class A) had approximately 40% higher budesonide AUC compared with healthy volunteers.

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Renal Impairment

Intact budesonide is not excreted renally. The main metabolites of budesonide, which have negligible corticosteroid activity, are largely (60%) excreted in urine.

Drug Interaction Studies

Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase plasma levels of budesonide.

Thus, clinically relevant drug interactions with potent CYP3A inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, cyclosporine, and grapefruit juice, are to be expected. Conversely, induction of CYP3A4 potentially could result in the lowering of budesonide plasma concentrations.

Effects of Other Drugs on Budesonide

Ketoconazole

In an open, non-randomized, cross-over study, 6 healthy subjects were given budesonide 10 mg as a single dose, either alone or concomitantly with the last ketoconazole dose of 3 days treatment with ketoconazole 100 mg twice daily. Co-administration of ketoconazole resulted in 8-fold the AUC of budesonide, compared to budesonide alone.

In an open, randomized, cross-over study 8 healthy subjects were given Entocort EC 3 mg as a single dose, either alone or concomitantly with the last ketoconazole dose of 4 days treatment with ketoconazole 200 mg once daily. Co-administration of ketoconazole resulted in 6.5-fold the AUC of budesonide, compared to budesonide alone.

Grapefruit Juice

In an open, randomized, cross-over study, 8 healthy subjects were given Entocort EC 3 mg, either alone, or concomitantly with 600 mL concentrated grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), on the last of 4 daily administrations. Concomitant administration of grapefruit juice resulted in doubling the bioavailability of budesonide compared to budesonide alone.

Proton Pump Inhibitors

The pharmacokinetics of TARPEYO have not been evaluated in combination with proton pump inhibitors (PPIs). Since the disintegration of TARPEYO is pH dependent, the release properties and uptake of budesonide may be altered when TARPEYO is taken after treatment with PPIs. In a study assessing intragastric and intraduodenal pH in healthy volunteers after repeated dosing with the PPI omeprazole 40 mg once daily, intragastric and intraduodenal pH did not exceed that required for disintegration of TARPEYO. Beyond the duodenum, PPIs such as omeprazole are unlikely to affect pH.

Oral Contraceptives (CYP3A4 Substrates)

In a parallel study, the pharmacokinetics of budesonide were not significantly different between healthy female subjects who received oral contraceptives containing desogestrel 0.15 mg and ethinyl estradiol 30 µg and healthy female subjects who did not receive oral contraceptives. Budesonide 4.5 mg once daily for one week did not affect the plasma concentrations of ethinyl estradiol, a CYP3A4 substrate. The effect of budesonide 16 mg once daily on the plasma concentrations of desogestrel and ethinyl estradiol was not studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with budesonide were conducted in rats and mice. In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.03 times the maximum recommended human dose (MRHD) on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.015 times the MRHD on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis). In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.03 times the MRHD of a body surface area basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 0.06 times the MRHD on a body surface area basis).

Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation (TK^{+/−}) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethal test, the rat hepatocyte UDS test and the mouse micronucleus test.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.05 times the MRHD on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal food consumption and body weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.012 times the MRHD on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.003 times the MRHD on a body surface area basis).

14 CLINICAL STUDIES

14.1 Treatment of IgAN

The effect of TARPEYO on proteinuria was assessed in a randomized, double-blind, multicenter study (Nef-301, 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 < 60 mL/min/1.73 m². The mean baseline UPCR was 1.6 g/g and 25% of patients had proteinuria > 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. The results are shown in Table 2.

Table 2: 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

TARPEYO (budesonide) delayed release capsules 4 mg, are white opaque- coated capsules marked with “CAL10 4 MG” in black ink on the body of the capsule. They are supplied as follows:

NDC 81749-004-01: Bottles of 120 capsules. Child-resistant cap.

Store at 20-25°C (68 - 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

Keep container tightly closed. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients that TARPEYO may cause hypercorticism and adrenal axis suppression and to follow a taper schedule, as instructed by their healthcare provider if discontinuing therapy [see *Warnings and Precautions* (5.1)].

TARPEYO causes immunosuppression. Advise patients to avoid exposure to people with chicken pox or measles and, if exposed, to consult their healthcare provider immediately. There is an increased risk of developing a variety of infections, including worsening of existing tuberculosis, fungal, bacterial, viral or parasitic infections, or ocular herpes simplex, and to contact their healthcare provider if they develop any symptoms of infection [see *Warnings and Precautions* (5.3)]. Provide advice regarding vaccination schedules for immunocompromised patients.

Advise patients that TARPEYO delayed release capsules should be swallowed whole and not chewed, crushed or broken and to take TARPEYO in the morning, at least 1 hour before a meal [See *Dosage and Administration* (2)].

Advise patients to avoid the consumption of grapefruit juice for the duration of their TARPEYO therapy [See *Drug Interactions* (7.1)].

TARPEYO is a registered trademark of Calliditas Therapeutics AB, or its affiliates.

© 2021 Calliditas Therapeutics AB (publ)

Manufactured for and distributed by:

Calliditas Therapeutics AB
Stockholm, Sweden

Patent: <http://www.calliditas.com/patents>

Patient Information
TARPEYO (tar-PAY-oh)
(budesonide)
delayed release capsules

What is TARPEYO?

TARPEYO is a prescription medicine used to reduce levels of protein in the urine (proteinuria) in adults with a kidney disease called primary immunoglobulin A nephropathy (IgAN), who are at high risk of disease progression.

It is not known if TARPEYO is safe and effective in children.

Do not take TARPEYO if you are allergic to budesonide or any of the ingredients in TARPEYO. See the end of this leaflet for a complete list of ingredients in TARPEYO.

Before taking TARPEYO, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems.
- plan to have surgery.
- have chickenpox or measles or have recently been near anyone with chickenpox or measles.
- have an infection.
- have high blood sugar levels (prediabetes or diabetes).
- have glaucoma or cataracts.
- have a family history of diabetes or glaucoma.
- have or have had tuberculosis.
- have high blood pressure (hypertension).
- have decreased bone mineral density (osteoporosis).
- have stomach ulcers.
- are pregnant or plan to become pregnant. TARPEYO may harm your unborn baby. Talk to your healthcare provider about the possible risk to your unborn baby if you take TARPEYO when you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if TARPEYO passes into your breast milk or if it will affect your baby. Talk to your healthcare provider about the best way to feed your baby during treatment with TARPEYO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TARPEYO and other medicines may affect each other causing side effects.

How should I take TARPEYO?

- Take TARPEYO exactly as your healthcare provider tells you.
- Your healthcare provider will decide how long you should take TARPEYO. Do not stop taking TARPEYO without first talking with your healthcare provider.
- Take your prescribed dose of TARPEYO 1 time each day in the morning, at least 1 hour before a meal.
- Take TARPEYO capsules whole. **Do not** open, chew, crush, or break TARPEYO capsules before swallowing.
- If you miss a dose of TARPEYO, take your prescribed dose at your next scheduled time. **Do not** take two doses of TARPEYO at the same time.
- If you take too much TARPEYO, call your healthcare provider right away or go to the nearest hospital emergency room.

What should I avoid while taking TARPEYO?

Do not eat grapefruit or drink grapefruit juice during your treatment with TARPEYO. Eating grapefruit or drinking grapefruit juice can increase the level of TARPEYO in your blood.

What are the possible side effects of TARPEYO?

TARPEYO may cause serious side effects, including:

- **Effects of having too much corticosteroid medicine in your blood (hypercorticism).** Long-time use of TARPEYO can cause you to have signs and symptoms of too much cortisol, a stress hormone in your blood. Tell your healthcare provider if you have any of the following signs and symptoms of hypercorticism:
 - o acne
 - o bruise easily
 - o rounding of your face (moon face)
 - o ankle swelling
 - o thicker or more hair on your body and face
 - o a fatty pad or hump between your shoulders (buffalo hump)
 - o pink or purple stretch marks on the skin of your abdomen, thighs, breasts, or arms
- **Adrenal suppression.** When TARPEYO is taken for a long period of time (chronic use), adrenal suppression can happen. This is a condition in which the adrenal glands do not make enough steroid hormones. Symptoms of adrenal suppression include:
 - o tiredness
 - o weakness
 - o nausea and vomiting
 - o low blood pressure

Tell your healthcare provider if you are under stress or have any symptoms of adrenal suppression during treatment with TARPEYO.

- **Risk of immunosuppression.** TARPEYO weakens your immune system. Taking medicines that weaken your immune system makes you more likely to get infections. Avoid contact with people who have contagious diseases, such as chickenpox or measles, during treatment with TARPEYO. Tell your healthcare provider right away if you come in contact with anyone who has chickenpox or measles. Consult with your healthcare provider regarding appropriate vaccination scheduling.
- Tell your healthcare provider if you develop any symptoms of infection during treatment with TARPEYO, including:
 - o fever
 - o feeling tired
 - o chills
 - o aches
 - o pain
 - o nausea and vomiting

The most common side effects of TARPEYO include:

- high blood pressure
- swelling of the lower legs, ankles, and feet
- muscle cramp
- acne
- irritation or inflammation of the skin
- weight increase
- shortness of breath
- swelling of the face
- indigestion
- tiredness
- thicker or more hair on your body and face

These are not all the possible side effects of TARPEYO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TARPEYO?

- Store TARPEYO at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TARPEYO in a tightly closed container.
- Protect from moisture.

Keep TARPEYO and all medicines out of the reach of children.

General information about the safe and effective use of TARPEYO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TARPEYO for a condition for which it was not prescribed. Do not give TARPEYO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TARPEYO that is written for health professionals.

What are the ingredients in TARPEYO?

Active ingredient: budesonide

Inactive ingredients: sugar spheres (sucrose and starch), hypromellose, polyethylene glycol, citric acid monohydrate, ethyl cellulose, medium chain triglycerides and oleic acid.

The capsules contain: hypromellose and titanium oxide (E171).

The printing ink on the capsules contain: shellac, propylene glycol and black iron oxide (E172).

The enteric coating on the capsules contain: methacrylic acid and methacrylate copolymer, talc and dibutyl sebacate.

Manufactured for and distributed by: Calliditas Therapeutics AB, Stockholm, Sweden

TARPEYO is a registered trademark of Calliditas Therapeutics AB, or its affiliates.

© 2021 Calliditas Therapeutics AB (publ)

Patent: <http://www.calliditas.com/patents>

For more information, go to www.TARPEYOTouchpoints.com or call 1-933-444-8277.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: 12/2021

Each delayed release capsule contains
4 mg of budesonide.

RECOMMENDED DOSAGE: See Prescribing
Information.

STORAGE: Keep container tightly closed.
Protect from moisture. **Do not store above
25°C (77°F); excursions permitted to 15°
to 30°C (59° to 86°F).** [See USP Controlled
Room Temperature].

Keep out of reach of children.

TARPEYO™ is a trademark of Calliditas
Therapeutics AB, or its affiliates.

Manufactured for and distributed by:
Calliditas Therapeutics AB,
Stockholm, Sweden

Reference ID: 4905283

NDC 81749-004-01

 **TARPEYO**™
(budesonide) delayed release capsules

4 mg

120 Capsules

Rx only

calliditas
THERAPEUTICS



70041629

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/

ALIZA M THOMPSON
12/15/2021 02:39:58 PM