09-J3000-09

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Reviewed: 06/11/25

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Subject: Tolvaptan (Jynarque®) Tablet

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Jynarque (tolvaptan) is an oral, selective vasopressin V2-receptor antagonist approved by the FDA in April 2018 to "slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)". Prior to FDA approval, Jynarque was granted orphan drug designation, as sponsor by the innovator drug company, for the treatment of ADPKD in April 2010. Jynarque is the first drug to be approved by the FDA for the management of patients with ADPKD. Tolvaptan inhibits vasopressin-stimulated cyst growth *in vitro* and chloride-dependent fluid secretion into cysts. In animal models, decreased cAMP concentrations are associated with decreases in the total kidney volume growth rate and the rate of formation and enlargement of kidney cysts. Tolvaptan, as brand name Samsca, was initially approved by the FDA in May 2009 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia. Samsca is initiated in a hospital setting due to frequent serum sodium monitoring requirements (to help prevent overly rapid correction and risk of osmotic demyelination). In addition, due to the risk of hepatic injury, tolvaptan use when treating hyponatremia is limited to no more than 30 days at a maximum dosage of 60 mg daily. Tolvaptan use in ADPKD requires continuous treatment at a higher dosage. As such, Jynarque is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program.

Polycystic kidney disease is an inherited disease that causes lifelong growth in kidney cysts and kidney volume, leading to progressive and irreversible decline in kidney function. It may be inherited as an autosomal dominant or recessive trait. The autosomal dominant form (ADPKD) is the most common genetic cause of chronic kidney disease. ADPKD occurs in all races and has a reported prevalence of 1:400 to 1:1,000. Most individuals eventually progress to end-stage renal disease (ESRD) requiring dialysis and/or kidney transplant. ADPKD is the underlying cause of kidney disease in approximately 5% of patients who initiate dialysis each year in the US. Renal function remains intact for most patients until the fourth decade of life; however, once the glomerular filtration rate (GFR) starts to decline, the

average reduction is about 4.5 mL/min per year. ADPKD is caused by two known (and possibly more unknown) genetic mutations: PKD1 and PKD2. The PKD1 mutations are more common (71% to 85%) than the PKD2 mutations (15%). Patients with PKD2 have a less severe phenotype (mean age of ESRD is 74 years) than those with PKD1 (54 years). Diagnosis primarily relies upon assessment of family history of ADPKD and imaging of the kidneys; ultrasonography is most commonly used. In patients with a family history, the number of renal cysts (depending on the patient's age) can generally confirm a diagnosis. However, genetic testing is the only way to establish a definitive diagnosis, and testing is particularly useful in patients without a family history of ADPKD. Genetic testing results are also useful in determining patients at higher risk for rapid progression to ESRD. Other characteristics such as kidney size and early onset of symptoms or hypertension are also useful predictors. The PROPKD (predicting renal outcomes in ADPKD) score is a recently developed scoring algorithm that stratifies ADPKD patients into low, intermediate, or high risk for rapid progression to ESRD. Prior to the approval of tolvaptan, there were no FDA-approved treatments for patients with ADPKD. Treatment included nonspecific measures, such as strict blood pressure control, dietary protein restriction, increased fluid intake, a low-salt diet, and statins (to reduce cardiovascular mortality). Once a patient progresses to ESRD the options are either dialysis or renal transplantation.

Jynarque was shown to slow the rate of decline in renal function in patients at risk of rapidly progressing ADPKD in two trials; TEMPO 3:4 in patients at earlier stages of disease and REPRISE in patients at later stages. The findings from these trials, when taken together, suggest that Jynarque slows the loss of renal function progressively through the course of the disease, and led to the approval by the FDA. In TEMPO 3:4, 1,445 adult patients with early (estimated creatinine clearance [≥60 mL/min), rapidly progressing (total kidney volume [TKV] ≥750 mL and age <51 years) ADPKD were randomized 2:1 to treatment with tolvaptan or placebo. Patients received treatment twice a day (first dose on waking, second dose approximately 9 hours later). Patients were initiated on 45 mg/15 mg, and up-titrated weekly to 60 mg/30 mg and then to 90 mg/30 mg as tolerated. Patients were to maintain the highest tolerated dose for 3 years. All patients were encouraged to drink adequate water to avoid thirst or dehydration and before bedtime. The primary endpoint was the difference for rate of change of TKV normalized as a percentage. The other key endpoints were ADPKD-related events and the slowing of EGFR during treatment. At baseline, average eGFR was 82 mL/min/1.73 m^2 and mean TKV was 1,692 mL (height adjusted 972 mL/m). The subjects' mean age was 39 years, 48% were female, and 84% were Caucasian. Of the 770 subjects who submitted to genetic analysis in TEMPO 3:4's open-label extension, 749 (97%) had an identifiable mutation in the PKD1 (656 or 88%), or PKD2 (93 or 12%) gene. The trial met its prespecified primary endpoint of 3-year change in TKV ($p<0.0001$). The difference in TKV between treatment groups mostly developed within the first year, the earliest assessment, with little further difference in years two and three. Tolvaptan has little effect on kidney size beyond what accrues during the first year of treatment. The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio, 0.87; 95% CI, 0.78 to 0.97; $p=0.0095$). The estimated difference in the annual rate of change in those who contributed to the analysis was 1.0 mL/min/1.73m^2/year (95% CI, 0.6 to1.4).

REPRISE was a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18 to 65) with CKD) with an eGFR between 25 and 65 mL/min/1.73m^2 if younger than age 56; or eGFR between 25 and 44 mL/min/1.73m^2, plus eGFR decline >2.0 mL/min/1.73m^2/year if between age 56 to 65. Subjects were to be treated for 12 months; after completion of treatment, patients entered a 3-

week follow-up period to assess renal function. The primary endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized by dividing by each subject's treatment duration. Prior to randomization, patients were required to complete sequential single-blind run-in periods during which they received placebo for 1 week, followed by tolvaptan titration for 2 weeks, and then treatment with tolvaptan at the highest tolerated dose achieved during titration for 3 weeks. During the titration period, tolvaptan was up-titrated every 3-4 days from a daily oral dose of 30 mg/15 mg to 45 mg/15 mg, 60 mg/30 mg and up to a maximum dose of 90 mg/30 mg. Only patients who could tolerate the two highest doses of tolvaptan (60 mg/30 mg or 90 mg/30 mg) for the subsequent 3 weeks were randomized 1:1 to treatment with tolvaptan or placebo. Patients were maintained on their highest tolerated dose for a period of 12 month. All patients were encouraged to start drinking an adequate amount of water at screening and continuing through the end of the trial to avoid thirst or dehydration. A total of 1519 subjects were enrolled in the study. Of these, 1370 subjects successfully completed the pre-randomization period and were randomized and treated during the 12-month double-blind period. Because 57 subjects did not complete the off-treatment follow-up period, 1313 subjects were included in the primary efficacy analysis. For subjects randomized, the baseline, average eGFR was 41 mL/min/1.73 m^2. Subjects' mean age was 47 years, 50% were female, and 92% were Caucasian. In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow-up was −2.3 mL/min/1.73 m2/year with tolvaptan as compared with −3.6 mL/min/1.73 m2/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m2/year ($p < 0.0001$). The key secondary endpoint (eGFR slope in ml/min/1.73 m2/year assessed using a linear mixed effect model of annualized eGFR (CKD-EPI)) showed a difference between treatment groups of 1.0 ml/min/ m2/year that was also statistically significant ($p < 0.0001$).

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of Jynarque (tolvaptan) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7")

1. Member has a diagnosis of autosomal dominant polycystic kidney disease (ADPKD)
2. The member is at high risk for rapid progression to end-stage renal disease (ESRD) as determined by their treating nephrologist
3. Member does not have stage 5 chronic kidney disease (CKD) and is not on dialysis
4. Treatment with Jynarque (tolvaptan) is prescribed by, or in consultation with, a specialist (e.g., nephrologist)
5. Member is 18 years of age or older
6. The member does not have any of the following FDA-labeled contraindications to Jynarque (tolvaptan) treatment ("a" to "g"):

a. A history, signs or symptoms of significant liver impairment or injury (does not apply to uncomplicated polycystic liver disease)
b. Taking strong CYP 3A inhibitors (e.g., clarithromycin, ketoconazole, ritonavir, voriconazole)
c. Uncorrected abnormal blood sodium concentrations
d. Unable to sense or respond to thirst
e. Hypovolemia
f. Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product
g. Uncorrected urinary outflow obstruction

7. **BOTH** of the following dosage limits ("a" and "b"):
   a. The initial dosage does not exceed 45 mg (AM dose)-15 mg (PM dose) per day
   b. After titration the maximum dosage does not exceed 90 mg (AM dose)-30 mg (PM dose) per day – must be achieved using the fewest number of tablets and blister cards possible

Approval duration: 6 months

Continuation of Jynarque (tolvaptan) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "5"):

1. An authorization or reauthorization for Jynarque (tolvaptan) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of autosomal dominant polycystic kidney disease (if another health plan, documentation of a health plan-paid claim for Jynarque during the 90 days immediately before the authorization request must be submitted); **OR** the member has previously met **ALL** indication-specific initiation criteria
2. Member has demonstrated a beneficial response to therapy (e.g., slowed kidney function decline, decreased kidney pain), **AND** the member has not progressed to end-stage renal disease (ESRD) that requires dialysis
3. Treatment with Jynarque (tolvaptan) is prescribed by, or in consultation with, a specialist (e.g., nephrologist)
4. The member does not have any of the following FDA-labeled contraindications to Jynarque (tolvaptan) treatment ("a" to "g"):
   a. A history, signs or symptoms of significant liver impairment or injury (does not apply to uncomplicated polycystic liver disease)
   b. Taking strong CYP 3A inhibitors (e.g., clarithromycin, ketoconazole, ritonavir, voriconazole)
   c. Uncorrected abnormal blood sodium concentrations
   d. Unable to sense or respond to thirst
   e. Hypovolemia
   f. Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product
   g. Uncorrected urinary outflow obstruction
5. The dosage of Jynarque (tolvaptan) does not exceed 90 mg (AM dose)-30 mg (PM dose) per day – must be achieved using the fewest number of tablets and blister cards possible

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)
- The initial dosage is 60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later. Titrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations. Patients may down-titrate based on tolerability. Encourage patients to drink enough water to avoid thirst or dehydration.

Dose Adjustments

- **Drug Interactions**: In patients taking concomitant moderate CYP 3A inhibitors (e.g., fluconazole), reduce the dose of as follows:
  - 90 mg and 30 mg – reduce to 45 mg and 15 mg
  - 60 mg and 30 mg – reduce to 30 mg and 15 mg
  - 45 mg and 15 mg – reduce to 15 mg and 15 mg

  Consider further reductions if patients cannot tolerate the reduced dose.

  Interrupt Jynarque temporarily for short term therapy with moderate CYP 3A inhibitors if the recommended reduced doses are not available.

  Use is contraindicated in patients taking strong CYP 3A inhibitors
- **Adverse Reactions**: At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue Jynarque, obtain repeat tests as soon as possible (within 48 to 72 hrs), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, Jynarque may be reinitiated with increased frequency of monitoring as long as ALT and AST remain below 3x ULN. Do not restart in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3x ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved. In patients with a stable, low baseline AST or ALT, an increase above 2x baseline, even if less than 2x ULN may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48- to 72 hrs) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.
- **Hepatic impairment**: Because of the risk of serious liver injury, use is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease which was present in 60% and 66% of patients in TEMPO 3:4 and REPRISE clinical trials, respectively.
- **Renal impairment**: Efficacy studies included patients with normal and reduced renal function. TEMPO 3:4 required patients to have an estimated creatinine clearance 60 mL/min, while REPRISE included patients with eGFRCKD-Epi 25 to 65 mL/min/1.73m^2. Data is not available for ADPKD patients with lower renal function.

Drug Availability

30 Count Bottles	NDC
15 mg	59148-082-13
30 mg	59148-083-13

Morning and Afternoon Doses	NCD	
	7-Day Blister Card (Containing 14 Tablets)	28-Day Carton (4 Blister Cards Containing a Total of 56 Tablets)
15 mg and 15 mg	59148-079-07	59148-079-28
30 mg and 15 mg	59148-080-07	59148-080-28
45 mg and 15 mg	59148-087-07	59148-087-28
60 mg and 30 mg	59148-088-07	59148-088-28
90 mg and 30 mg	59148-089-07	59148-089-28

PRECAUTIONS:

Boxed Warning

- **WARNING: RISK OF SERIOUS LIVER INJURY**
  - Jynarque (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported.
  - Measure ALT, AST and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.
  - Because of the risks of serious liver injury, Jynarque is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program.

Contraindications

- Patient with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease.
- Patients taking strong CYP 3A inhibitors
- Patients with uncorrected abnormal blood sodium concentrations
- Patients unable to sense or respond to thirst
- Patients with hypovolemia
- Patients with hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product
- Patients with uncorrected urinary outflow obstruction
- Patients with anuria

Precautions/Warnings

- **Serious Liver Injury** – Jynarque can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus,

dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiation of Jynarque, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

- **Jynarque REMS Program** - Jynarque is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program, because of the risks of liver injury. Notable requirements include the following:
    - Prescribers must be certified by enrolling in the REMS program
    - Prescribers must inform patients receiving Jynarque about the risk of hepatotoxicity associated with its use and how to recognize the signs and symptoms of hepatotoxicity and the appropriate actions to take if it occurs
    - Patients must enroll in the REMS program and comply with ongoing monitoring requirements
    - Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive Jynarque.

  Further information, including a list of qualified pharmacies/distributors, is available at www.JYNARQUEREMS.com or by telephone at 1-877-726-7220.
- **Hypernatremia, Dehydration and Hypovolemia** - Jynarque increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypernatremia. Therefore, ensure abnormalities in sodium concentrations are corrected prior to initiation of therapy. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. In the two double-blind, placebo-controlled trials of patients with ADPKD, hypernatremia (defined as any serum sodium concentration >150 mEq/L) was observed in 4.0% vs. 0.6% and 1.4% vs. 0% of tolvaptan-treated vs. placebo-treated patients, respectively. The rate of dehydration and hypovolemia in the two studies was 2.1% vs. 0.7% and 2.3% vs. 0.4% for tolvaptan-treated versus placebo-treated patients, respectively. If serum sodium increases above normal range or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, then suspend treatment until serum sodium, hydration status and volume status is within the normal range.
- **Co-Administration with Inhibitors of CYP 3A** - Concomitant use of Jynarque with drugs that are moderate or strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP 3A inhibitors is contraindicated; dose reduction of Jynarque is recommended for patients while taking moderate CYP 3A inhibitors.
- **Co-Administration with V2-Receptor Agonist** - As a V2-receptor antagonist, tolvaptan will interfere with the V2-agonist activity of desmopressin. Avoid concomitant use of Jynarque with a V2-agonist.
- **Pregnancy** - Available data with Jynarque use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. Advise pregnant women of the potential risk to the fetus.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

Q61.2	Polycystic kidney, adult type

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

PROPKD Scoring Algorithm and Risk Categories

Variable	Category	Points
Biological sex	Female	0
	Male	1
Hypertension before 35 years of age	No	0
	Yes	2
At least one urological complication* before 35 years of age	No	0
	Yes	2
Mutation type	*PKD2*	0
	PKD1/Non-Truncating	2
	P*KD1*/Truncating	4

Risk Categories:

- Low risk: 0 to 3 points
- Intermediate risk: 4 to 6 points
- High risk: 7 to 9 points

*Qualifying complications include hematuria, cyst infection, and cyst-related flank pain

REFERENCES:

1. Bolignano D, Palmer SC, Ruospo M, et al. Interventions for preventing the progression of autosomal dominant polycystic kidney disease. Cochrane Database Syst Rev. 2015 Jul 14;(7):CD010294.
2. Chapman AB, Devuyst O, Eckardt KU, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2015 Jul;88(1):17-27. Epub 2015 Mar 18.
3. Chebib FT, Perrone RD, Chapman AB, et al. A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. J Am Soc Nephrol. 2018 Oct;29(10):2458-2470.
4. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2023. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 5/27/25.
5. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. Lancet. 2019 Mar 2;393(10174):919-935.
6. Cornec-Le Gall E, Audrézet MP, Rousseau A, et al. The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease. J Am Soc Nephrol. 2016 Mar;27(3):942-51. Epub 2015 Jul 6.
7. Cornec-Le Gall E, Blais JD, Irazabal MV, et al. Can we further enrich autosomal dominant polycystic kidney disease clinical trials for rapidly progressive patients? Application of the PROPKD score in the TEMPO trial. Nephrol Dial Transplant. 2017 Jul 19. [Epub ahead of print].
8. Dudley J, Winyard P, Cuthell O, et al. Clinical practice guideline monitoring children and young people with, or at risk of developing autosomal dominant polycystic kidney disease (ADPKD). BMC Nephrology. 2019; 20:148.
9. Edwards ME, Chebib FT, Irazabal MV, et al. Long-Term Administration of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease. Clin J Am Soc Nephrol. 2018 Jul 19. pii: CJN.01520218 [Epub ahead of print].
10. Gansevoort RT, Arici M, Benzing T, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. Nephrol Dial Transplant. 2016;31(3):337-48.
11. Harris T, Sandford R, de Coninck B, et al. European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care: European ADPKD Forum and Multispecialist Roundtable participants. Nephrol Dial Transplant. 2017 Dec 22. [Epub ahead of print].
12. Horie S, Mochizuki T, Muto S, et al. Evidence-based clinical practice guidelines for polycystic kidney disease 2014. Clin Exp Nephrol. 2016 Aug;20(4):493-509.
13. Jynarque (tolvaptan) package insert. Tokyo, Japan: Otsuka Pharmaceutical Co; March 2025.
14. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 5/27/25.
15. Müller RU, Haas CS, and Sayer JA. Practical approaches to the management of autosomal dominant polycystic kidney disease patients in the era of tolvaptan. Clin Kidney J. 2018 Feb;11(1):62-69. Epub 2017 Jul 27.

16. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 2025 May 27]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
17. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009 Jan;20(1):205-12. Epub 2008 Oct 22.
18. Soroka S, Alam A, Bevilacqua M, et al. Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease. Can J Kidney Health Dis. 2018; 5: 2054358118801589.
19. Torres VE, Chapman AB, Devuyst O, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial. Nephrol Dial Transplant. 2018 Mar 1;33(3):477-489.
20. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2017 Nov 16;377(20):1930-1942. Epub 2017 Nov 4.
21. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012 Dec 20;367(25):2407-18. Epub 2012 Nov 3.
22. Torres VE, Higashihara E, Devuyst O, et al. Effect of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease by CKD Stage: Results from the TEMPO 3:4 Trial. Clin J Am Soc Nephrol. 2016 May 6;11(5):803-11. Epub 2016 Feb 23.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/11/25.

GUIDELINE UPDATE INFORMATION:

09/15/18	New Medical Coverage Guideline.
08/15/19	Review and revision to guideline consisting of updating the description section, position statement, and references.
08/15/20	Review and revision to guideline consisting of updating the position statement and references.
08/15/21	Review and revision to guideline consisting of updating the dosage/administration, warnings/precautions, and references.
08/15/22	Review and revision to guideline consisting of updating the references.
08/15/23	Review and revision to guideline consisting of updating the references.
07/15/24	Review and revision to guideline consisting of updating the references.
07/01/25	Review and revision to guideline consisting of revising the position statement to remove documentation requirements, changing kidney function requirements to no stage 5 CKD or dialysis, and expanding specialist prescribers and updating the references.