Jynarque Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
07-01-2024	10-01-2018

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Jynarque® (tolvaptan) Tablet	To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

ADPKD	Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney disease that affects approximately 12.5 million people worldwide. Mutations in two genes have been identified to be the major cause of ADPKD. Mutations in the PKD1 gene (located on chromosome 16) account for 85% of cases, while mutations in the PKD2 gene (located on chromosome 4) account for 15% of cases. ADPKD is a systemic disorder characterized by continuous cyst development and growth within the kidneys and other organs, leading to numerous clinical manifestations. End stage renal disease ensues, typically after the fourth decade of life.(2-4)
	
	Widely accepted practice guidelines do not currently exist for ADPKD diagnosis, evaluation, prevention, and treatment. Multiple guidelines offer similar diagnostic criteria.
	
	• American Academy of Family Physicians(3)
	  ○ Ultrasonography is the preferred screening method due to increased availability, lower cost, and lack of radiation exposure, although magnetic resonance imaging (MRI) and computed tomography (CT) are slightly more sensitive
	  ○ Ultrasonography (at-risk ADPKD type 1)
	  ▪ Less than 30 years of age: greater than or equal to 2 cysts in one kidney or both kidneys
	  ▪ 30-59 years of age: greater than or equal to 2 cysts in each kidney
	  ▪ 60 years of age and older: greater than or equal to 4 cysts in each kidney
	  ○ Ultrasonography (at-risk and unknown genotype)
	  ▪ 15-39 years of age: greater than or equal to 3 cysts in one or both kidneys
	  ▪ 40-59 years of age: greater than or equal to 2 cysts in each kidney
	  ▪ 60 years of age and older: greater than or equal to 4 cysts in each kidney

	○ MRI (at-risk) ▪ Less than 30 years of age: greater than or equal to 5 cysts in each kidney ▪ 30-44 years of age: greater than or equal to 6 cysts in each kidney ▪ 45-59 years of age (females): greater than 6 cysts in each kidney ▪ 45-59 years of age (males): greater than 9 cysts in each kidney ○ Genetic testing is not standard practice, but is useful in certain scenarios, such as unknown family history with findings of enlarged kidneys with renal cysts, or at-risk patient wishing to be a kidney donor • Autosomal Dominant Polycystic Kidney Disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference(2) ○ Asymptomatic patients - screening with renal ultrasonography is usually used because it is inexpensive and widely available ▪ At-risk patients (defined as first-degree relatives of individuals diagnosed or suspected to have ADPKD) • Children: screening is not currently recommended • Ultrasonography for diagnosis of ADPKD ○ 15-39 years of age: a total of greater than or equal to 3 renal cysts (unilateral or bilateral) ○ 40-59 years of age: greater than or equal to 2 renal cysts in each kidney • Ultrasonography can also be used for exclusion of ADPKD ○ 40 years of age and older: absence of any renal cyst • MRI can be used for exclusion of ADPKD ○ 40 years of age or younger: less than 5 renal cysts ○ Genetic testing is not required but may be considered in patients with equivocal or atypical renal finding, marked discordant disease within family, very mild PKD, sporadic PKD with no family history, reproductive counseling, and early and severe PKD or PKD with syndromic features • A panel of Canadian nephrologists developed the following updated recommendations for assessing the risk of disease progression and pharmacological management of patients with ADPKD based on evidence published since the development of the first consensus recommendation(4) ○ Identifying patient with ADPKD ▪ Patients should be referred to a nephrologist for initial assessment. Initial assessment should include kidney imaging and, in some cases, genetic testing to determine the patient's risk of rapid progression and to determine what treatment should be initiated. ○ Renal imaging for diagnosis, prognosis, and disease progression ▪ The preferred method for confirming the presence of ADPKD in patients with a family history is ultrasounds imaging and the use of the Unified Criteria to establish diagnosis and determine if typical or atypical. ▪ In select circumstances, such as in patients without a family history of ADPKD, other imaging modalities, including CT or MRI, may be considered to diagnose ADPKD, particularly to detect cysts in younger patients. ▪ A baseline assessment of renal size should be undertaken in patients with ADPKD. The objective of these measurements is to determine which patients are suitable candidates to be considered for therapeutic intervention based on their risk of progression.

	▪ In patients with typical morphology, use US to measure kidney length (KL), or MRI or CT to measure total kidney volume (TKV) (and to calculate height adjusted TKV [htTKV] where appropriate) if a more precise measurement is required for therapeutic decisions. In cases where historical images are available, those images should be consulted before requesting new imaging. ▪ After a baseline assessment of renal size, not all patients require routine reassessment of renal size. If renal size reassessment is done, it should not exceed a frequency of once yearly. o Assessing disease progression ▪ In current clinical practice, patients with a htTKV measurement are categorized in terms of their risk of progression as per the Mayo Clinic classification or other validated clinical tools (e.g., PROPKD scoring, genetic scoring). ▪ Currently available TKV-based prognostication tools should be applied only to class 1 (typical morphology) patients, as these patients are likely to be rapid progressors. Certain patients may require further clinical evaluation. ▪ Patients should be considered at risk of rapid progression of ADPKD renal disease if they meet either of the following criteria: 1) classified as Mayo class 1C, 1D, or 1E, or 2) have an US KL of greater than 16.5 cm bilaterally. ▪ Suggest the following be used as markers of rapid progression: 1) a sequential increase of greater than 5% annually in htTKV on imaging, or 2) documented disease progression (e.g., rapid decline in eGFR, defined as decline in eGFR greater than 2.5 mL/min/1.73 m^2 annually; patients in the placebo group of the TEMPO 3:4 study showed an annual decline in eGFR of 3.5 mL/min/1.73 m^2 over the three years of observation). o ADPKD-specific treatment options ▪ Treatment with tolvaptan for patients who fulfill the enrollment criteria of the TEMPO 3:4 study: • 18 to 50 years of age with TKV greater than 750 mL and eGFR greater than 45 mL/min/1.73 m^2 ▪ Treatment with tolvaptan for patients who fulfill the enrollment criteria of the REPRISE study: • 18 to 55 years of age with eGFR of 25 to 65 mL/ min/1.73 m^2 • 56 to 65 years of age with eGFR of 25 to 44 mL/ min/1.73 m^2 with historical evidence of a decline in eGFR >2.0 mL/min/1.73 m^2 /year • We believe that, although there were no inclusion criteria for kidney size, based on the abundance of evidence that increased size of kidneys is relevant, these REPRISE criteria relate to those patients with ADPKD who have enlarged kidneys. In those patients with advanced or rapidly progressive CKD without enlarged kidneys, an alternate diagnosis for CKD should be investigated. ▪ Suggest treatment with tolvaptan for patients who, according to the Mayo Classification, are classified as 1D or 1E with eGFR in CKD stages 1-4 (eGFR greater than 25 mL/min). Treatment with tolvaptan may be considered for patients who are classified as 1C and are younger than 50 years old or have other risk factors for rapid progression (such as an annual decrease in eGFR of >2.5 mL/min/1.73 m^2 and/or increase in TKV of >5% per year).

Efficacy	Tolvaptan 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.(1) TEMPO 3:4 was a phase 3, double-blind, placebo-controlled, randomized trial which included 1445 adult patients (age greater than 18 years) with early (estimated creatinine clearance [eCrCl] greater than or equal to 60 mL/min), rapidly progressing (TKV greater than or equal to 750 mL and age less than 51 years) ADPKD (diagnosed by modified Ravine criteria). The trial met its prespecified primary endpoint of 3-year change in TKV (p less than 0.0001). Over the 3-year period, TKV increased by 2.8% per year (95% confidence interval [CI], 2.5 to 3.1) with tolvaptan versus 5.5% per year (95% CI, 5.1 to 6.0) with placebo. 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).(1) REPRISE was a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18-65) with chronic kidney disease (CKD) with an eGFR between 25 and 65 mL/min/1.73 m^2 if younger than age 56; or eGFR between 25 and 44 mL/min/1.73 m^2, plus eGFR decline greater than 2.0 mL/min/1.73 m^2/year if between age 56-65. 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 change of eGFR from pretreatment baseline to post-treatment follow-up was – 2.3 mL/min/1.73 m^2/year with tolvaptan as compared with – 3.6 mL/min/1.73 m^2/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m^2/year (p less than 0.0001). The key secondary endpoint (eGFR slope in ml/min/1.73 m^2/year assessed using a linear mixed effect model of annualized eGFR (CKD-EPI)) showed a difference between treatment groups of 1.0 ml/min/m^2/year that was also statistically significant (p less than 0.0001).(1)
Safety	Jynarque has the following boxed warnings:(1) • Jynarque 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 continuing 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. • Jynarque is available only through a restricted distribution program called the Jynarque REMS Program Jynarque has the following contraindications:(1) • History of signs or symptoms of significant liver impairment or injury, does not include uncomplicated polycystic liver disease • Concomitant use with strong CYP 3A inhibitors • Uncorrected abnormal blood sodium concentrations • Unable to sense or respond to thirst • Hypovolemia • Hypersensitivity to tolvaptan or components of the product • Uncorrected urinary outflow obstruction • Anuria

REFERENCES

Number	Reference
1	Jynarque prescribing information. Otsuka America Pharmaceuticals, Inc. October 2020.
2	Chapman, A.B., Devuyst, O., Eckardt, K.-U., Gansevoort, R. T., Harris, T., Horie, S., Kasiske, B. L., Odland, D., Pei, Y., Perrone, R. D., Pirson, Y., Schrier, R. W., Torra, R., Torres, V. E., Watnick, T., &

Number	Reference
	Wheeler, D. C. (2015). Autosomal-dominant polycystic kidney disease (ADPKD): Executive summary from a kidney disease: Improving global outcomes (KDIGO) controversies conference. *Kidney International*, *88*(1), 17–27. https://doi.org/10.1038/ki.2015.59
3	Srivastava, A., Patel, N., Autosomal dominant polycystic kidney disease. *American Academy of Family Physician*. 2014;90(5):303-307.
4	Soroka, S., Alam, A., Bevilacqua, M., Girard, L.-P., Komenda, P., Loertscher, R., McFarlane, P., Pandeya, S., Tam, P., & Bichet, D. G. (2018). Updated Canadian expert consensus on assessing risk of disease progression and pharmacological management of autosomal dominant polycystic kidney disease. *Canadian Journal of Kidney Health and Disease*, *5*, 205435811880158. https://doi.org/10.1177/2054358118801589

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Jynarque	tolvaptan tab therapy pack	15 MG ; 30 & 15 MG ; 45 & 15 MG ; 60 & 30 MG ; 90 & 30 MG	M ; N ; O ; Y	N		
Jynarque	tolvaptan tab	15 MG ; 30 MG	M ; N ; O ; Y	N ; O ; Y		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Jynarque	tolvaptan tab	15 MG	60	Tablets	30	DAYS			59148008213
Jynarque	tolvaptan tab	30 MG	30	Tablets	30	DAYS			59148008313
Jynarque	Tolvaptan Tab Therapy Pack 15 MG	15 MG	56	Tablets	28	DAYS			
Jynarque	Tolvaptan Tab Therapy Pack 30 & 15 MG	30 & 15 MG	56	Tablets	28	DAYS			
Jynarque	Tolvaptan Tab Therapy Pack 45 & 15 MG	45 & 15 MG	56	Tablets	28	DAYS			
Jynarque	Tolvaptan Tab Therapy Pack 60 & 30 MG	60 & 30 MG	56	Tablets	28	DAYS			
Jynarque	Tolvaptan Tab Therapy Pack 90 & 30 MG	90 & 30 MG	56	Tablets	28	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Jynarque	tolvaptan tab	15 MG ; 30 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jynarque	tolvaptan tab therapy pack	15 MG ; 30 & 15 MG ; 45 & 15 MG ; 60 & 30 MG ; 90 & 30 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Jynarque	tolvaptan tab	30 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jynarque	tolvaptan tab	15 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jynarque	Tolvaptan Tab Therapy Pack 15 MG	15 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jynarque	Tolvaptan Tab Therapy Pack 30 & 15 MG	30 & 15 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jynarque	Tolvaptan Tab Therapy Pack 45 & 15 MG	45 & 15 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jynarque	Tolvaptan Tab Therapy Pack 60 & 30 MG	60 & 30 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jynarque	Tolvaptan Tab Therapy Pack 90 & 30 MG	90 & 30 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) and BOTH of the following: A. The patient does not have stage 5 chronic kidney disease (CKD) **AND** B. The patient is not on dialysis **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient will NOT be using the requested agent in combination with another tolvaptan agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient will NOT be using the requested agent in combination with another tolvaptan agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months