The earlier ADPKD is identified, the quicker a treatment plan can be put into place[1]

For your patients at risk for rapidly progressing ADPKD,

JYNARQUE® (tolvaptan) could change the course of their disease

A disease-modifying treatment[2]—JYNARQUE is the first and only FDA-approved medicine indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD.

ADPKD=autosomal dominant polycystic kidney disease.

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 transaminases (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 Risk Evaluation and Mitigation Strategy program called the JYNARQUE REMS Program

Please see **IMPORTANT SAFETY INFORMATION** on pages 8-9.

JYNARQUE®
(tolvaptan)
15, 30, 45, 60, 90 mg tablets

What is autosomal dominant polycystic kidney disease (ADPKD)?

ADPKD is a disease that causes cysts to form and grow in the kidney, eventually impairing kidney function. Over time, enlarging cysts can increase kidney size by up to 4 times that of normal kidneys[3,4]

4th
leading cause of end-stage kidney disease (ESKD)[5]

A person diagnosed with ADPKD has a
50%
chance of passing the disease on to their children[6]

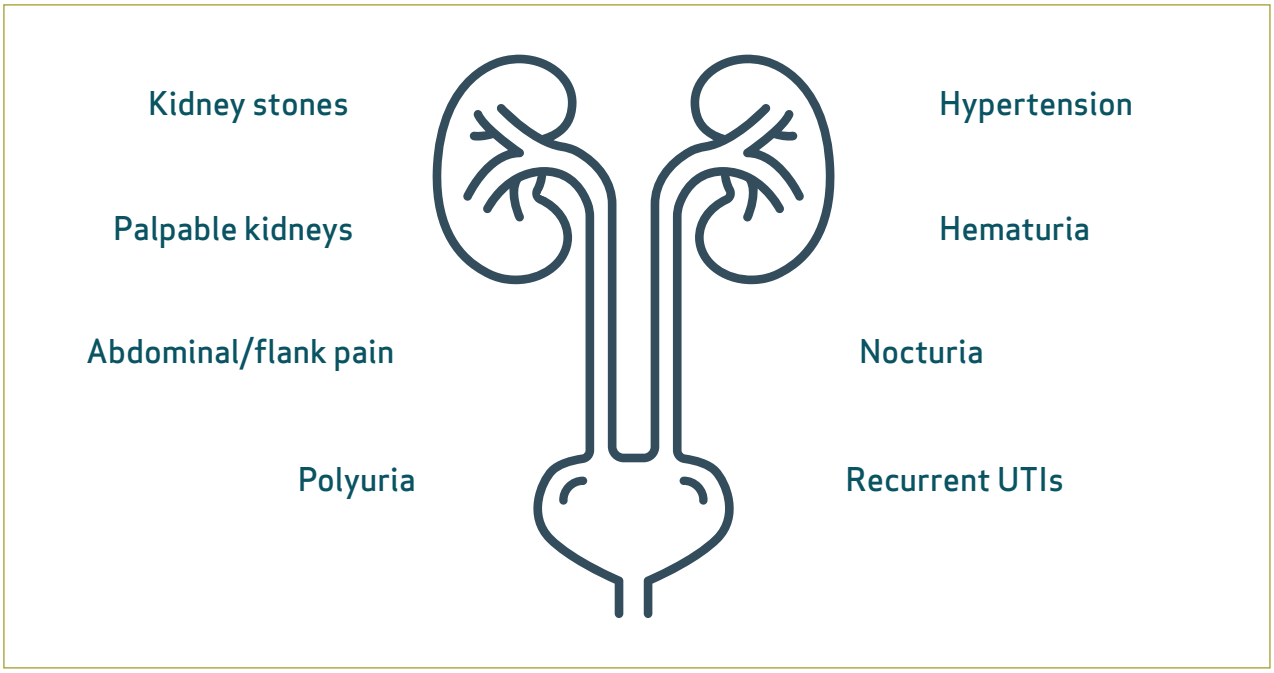
~1 in 2
ADPKD patients will reach **ESKD by age 60**, which leads to dialysis or a kidney transplant[7]

- ADPKD is a genetic, progressive disease characterized by the continuous development and enlargement of cysts in the kidneys[3,8]
  - —While ADPKD is genetic, the rate of progression is variable, even in the same family[5,9]

ADPKD is a rare disease that may not be promptly recognized when patients experience symptoms. As a result, years can pass before a diagnosis is made[10]

Early identification of ADPKD is important[10]

Even though eGFR may remain stable, cyst growth and kidney enlargement are associated with multiple symptoms and can damage the kidneys[11,12]



eGFR=estimated glomerular filtration rate; KDIGO=Kidney Disease: Improving Global Outcomes; UTI=urinary tract infection.

Patients with ADPKD may remain asymptomatic for years while the disease progresses[10]

There are multiple techniques that can be used to confirm a diagnosis[13]

- Diagnosis of ADPKD is typically established on the basis of:

Positive family history

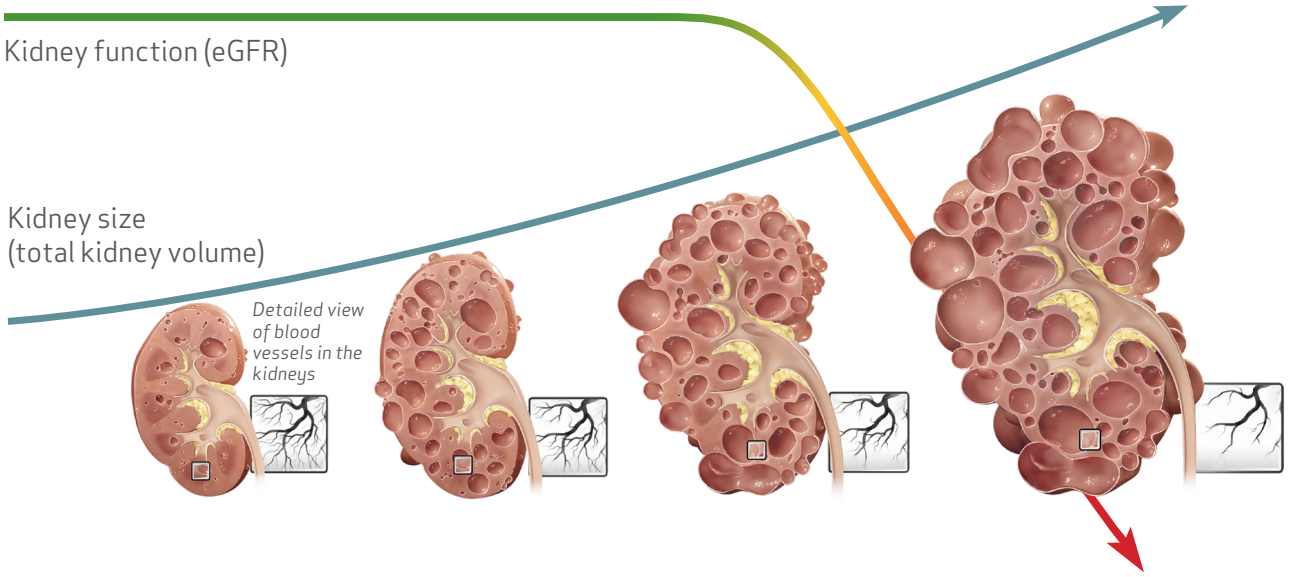
Imaging studies

Ultrasound is the most commonly used imaging modality for a diagnosis of ADPKD[14]

KDIGO Guidelines recommend referring your patients who have hereditary kidney function disease, like ADPKD, to a nephrologist[1]

ADPKD can be rapidly progressing, even if eGFR appears normal or slightly reduced[4]

Changes in kidney size often precede kidney function decline[15,16]



Adapted from Grantham JJ, et al. *Nat Rev Nephrol*. 2011;7(10):556-566.

Patients presenting with a rapid decline in eGFR are already experiencing rapid disease progression[1,17]*

*eGFR decline of ≥5 mL/min/1.73 m^2 within 1 year or eGFR decline of ≥2.5 mL/min/1.73 m^2 per year over a period of 5 years.[17]

The rate of progression of ADPKD is highly variable[5]

- Rapid progression of ADPKD can start as early as CKD Stage 1[17]
- Patients with ADPKD may remain asymptomatic for years while the disease progresses, likely due to compensatory hyperfiltration[10,15]
- Healthy nephrons compensate for damaged nephrons in the early stages of ADPKD, causing eGFR to appear normal or slightly reduced, despite the fact that damage is occurring[6,16]

Refer your patients to a nephrologist if you identify these risk factors associated with risk of rapid progression[1]

Don't wait for rapidly declining eGFR to take action—If a patient presents with any of these independently validated risk factors, they could be appropriate for treatment[18]

TKV greater than expected for age[19,20]

Kidney size has been shown to be a strong predictor of the rate of ADPKD progression[21]

Overweight and obesity (BMI ≥25 kg/m²)[22]

Family history of ESKD at or before age 58[17]

Hypertension before age 35[23]

Urologic events before age 35[23]

(gross hematuria, cyst infection, or flank pain related to cysts)

Proteinuria and microalbuminuria[18]

Truncating *PKD1* mutation[23]

BMI=body mass index; CKD=chronic kidney disease; TKV=total kidney volume.

KDIGO Guidelines recommend referring your patients who have hereditary kidney function disease, like ADPKD, to a nephrologist[1]

A disease-modifying treatment[2]—JYNARQUE® (tolvaptan) slows the decline of kidney function by decreasing the rate of cyst growth[3]

REPRISE Trial[24,25] — **A 12-month trial of patients with CKD late Stage 2 to early Stage 4**

35% reduction in decline of kidney function vs placebo

Treatment effect: 1.3 mL/min/1.73 m^2/year (95% CI: 0.86 to 1.68; *P*<0.0001)

REPRISE was a double-blind, placebo-controlled randomized withdrawal trial of 1370 patients with ADPKD. The inclusion criteria were: 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 >2.0 mL/min/1.73 m^2/year if between ages 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 primary endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized by dividing each subject's treatment duration.**[24,26]

TEMPO 3:4 Trial[3,27] — **A 36-month trial in patients with CKD Stages 1, 2, and 3**

49% reduction of TKV vs placebo at the end of 3 years*

Month 36 treatment effect: -9.2% (*P*<0.001)

The difference in TKV between treatment groups was most prominent within the first year, at the earliest assessment; the difference was minimal in years 2 and 3. JYNARQUE had little effect of kidney size beyond what accrued during the first year of treatment.†

TEMPO 3:4 was a double-blind, placebo-controlled randomized trial of 1445 patients with ADPKD. The inclusion criteria were: 18 to 50 years of age; early, rapidly progressing ADPKD (meeting modified Ravine criteria‡); TKV ≥750 mL; creatinine clearance ≥60 mL/min. Patients were treated for up to 3 years. **The primary endpoint was annual rate of change in the total kidney volume.**[3]

*Data only included those patients who remained in the study for 3 years; effect in those who discontinued is unknown.[3]

†In years 4 and 5 during the TEMPO 3:4 extension trial, both groups received JYNARQUE and the difference between the groups in TKV was not maintained.

‡Ravine criteria defined as at least 2 unilateral or bilateral kidney cysts in at-risk individuals between 15 and 30 years of age; 2 cysts in each kidney in individuals between 30 and 59 years of age; and at least 4 cysts in each kidney in individuals older than 60 years of age.[28,29]

SELECT IMPORTANT SAFETY INFORMATION:

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

Please see **IMPORTANT SAFETY INFORMATION** on pages 8-9.

Clinical safety profile of JYNARQUE® (tolvaptan)

JYNARQUE has been studied in the 2 largest clinical trials of over 2800 patients with ADPKD across CKD stages 1–4[3,24,30]

TEMPO 3:4—Treatment-emergent adverse reactions in ≥3% of JYNARQUE-treated patients with risk difference ≥1.5%, randomized period		
Adverse reaction	**Percentage of patients reporting reaction**	
	JYNARQUE (n=961)	**Placebo (n=483)**
Increased urination[§]	**69.5**	**28.0**
Thirst[‖]	**63.7**	**23.4**
Dry mouth	**16.0**	**12.4**
Fatigue	**13.6**	**9.7**
Diarrhea	**13.3**	**11.0**
Dizziness	**11.3**	**8.7**
Dyspepsia	**7.9**	**3.3**
Decreased appetite	**7.2**	**1.0**
Abdominal distension	**4.9**	**3.3**
Dry skin	**4.9**	**1.7**
Rash	**4.2**	**1.9**
Hyperuricemia	**3.9**	**1.9**
Palpitations	**3.5**	**1.2**

Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

- The REPRISE trial employed a 5-week single-blind titration and run-in period for JYNARQUE prior to the randomized double-blind period. During the JYNARQUE titration and run-in period, 126 (8.4%) of the 1496 patients discontinued the study, 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse reaction rates observed during the randomized period are not described
- In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (4.9 % [80/1637] vs 1.1 % [13/1166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug

ALT=alanine aminotransferase; CI=confidence interval; REPRISE=Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy; TEMPO=Tolvaptan Efficacy and Safety Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; ULN=upper limit of normal.

[§]Increased urination includes micturition urgency, nocturia, pollakiuria, and polyuria.

[‖]Thirst includes polydipsia and thirst.

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INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE® (tolvaptan)

INDICATION:

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

IMPORTANT SAFETY INFORMATION:

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 transaminases (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 Risk Evaluation and Mitigation Strategy program called the JYNARQUE REMS Program**

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

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 initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

IMPORTANT SAFETY INFORMATION (cont'd)

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. 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. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients taking moderate CYP3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE.

Adverse Reactions: Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

Other Drug Interactions:

- **Strong CYP3A Inducers:** Co-administration with strong CYP3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP3A inducers
- **V_2-Receptor Agonist:** Tolvaptan interferes with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist

Pregnancy and Lactation: Based on animal data, JYNARQUE may cause fetal harm. In general, JYNARQUE should be discontinued during pregnancy. Advise women not to breastfeed during treatment with JYNARQUE.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see FULL PRESCRIBING INFORMATION, including **BOXED WARNING**.

The earlier ADPKD is identified, the quicker a treatment plan can be put into place[1]

If you recognize any of these patient types in your practice, refer them to a nephrologist to determine if they are appropriate for JYNARQUE® (tolvaptan)

Bob, 53—Stage 3A CKD

His rapidly declining kidney function is evidence of rapidly progressing ADPKD[1,17]

Tim, 31—Stage 2 CKD

Tim's positive family history puts him at risk of rapidly progressing ADPKD as his father developed ESKD at age 54[17]

Julia, 40—Stage 2 CKD

Her hypertension, obesity, and family history are signs of rapidly progressing ADPKD[17,22,23]

Patient images and patient cases are fictional.

REMS=Risk Evaluation and Mitigation Strategy.

Click here to find a REMS-certified prescriber

If you would like to talk to a local representative for JYNARQUE over the phone, please call 833-4-OTSUKA (833-468-7852).

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