For your patients at risk for rapidly progressing ADPKD,

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

A disease-modifying treatment[1]—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 24-25.

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

Once you've confirmed a patient's ADPKD diagnosis

Taking a holistic assessment can identify appropriate patients for JYNARQUE® (tolvaptan)

Does your patient have rapidly declining eGFR?[2]

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

Yes

Evidence of rapidly progressing ADPKD

Could be an appropriate patient for **JYNARQUE**

No

While eGFR appears normal, it may not be telling the whole story

There is a significant delay between when evidence of kidney function decline is visible and when kidney damage has occurred[3]

Kidney size is a strong predictor of risk of rapid progression before eGFR begins to decline[3,4]

eGFR appears normal

Gold Standard Method[5]

Total kidney volume (TKV)*

MRI/CT reliably measures kidney size to calculate TKV[6,7]

Use htTKV and age to plot along the Mayo Classification chart—a patient in Class 1C, 1D, or 1E is at high risk of rapid progression[6,7]

If yes — Could be an appropriate patient for **JYNARQUE**

Kidney length[2,6†]

When MRI/CT-calculated TKV is not available, ultrasound can be used to measure kidney length

>16.5 cm at <45 years means patient is at risk of rapid progression

If yes — Could be an appropriate patient for **JYNARQUE**

Other factors

Be on the lookout for any ONE of these independently validated risk factors associated with rapid progression[2,8-10]:

- Truncating *PKD1* mutation
- Overweight and obesity, BMI ≥25 kg/m^2
- Hypertension before age 35
- Urologic events before age 35 (gross hematuria, cyst infection, or flank pain related to cysts)
- Proteinuria and microalbuminuria
- Family history of ESKD at or before age 58

If yes — Could be an appropriate patient for **JYNARQUE**

Physician should use their clinical judgment when assessing each patient for treatment with JYNARQUE.

CKD=chronic kidney disease; CT=computed tomography; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; htTKV =height-adjusted total kidney volume; MRI=magnetic resonance imaging.

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 24-25.

*Identifying a TKV greater than expected for your patient's age can provide an early and reliable marker for rapid disease progression in ADPKD.[11,12]

†A kidney length of >16.5 cm was shown to predict development of CKD Stage 3 within 8 years in patients with ADPKD who were <45 years of age and who had CKD Stage 1 or 2.[4]

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ADPKD is a genetic, progressive disease characterized by the continuous development and enlargement of cysts in the kidneys[13,14]

In ADPKD, cysts enlarge the kidneys and impair their ability to function normally[15]

The **rate of progression** in ADPKD is variable, even within the same family[16,17]

4th leading cause of ESKD[16]

~1 in 2
ADPKD patients will reach **ESKD by age 60**, which leads to dialysis or a kidney transplant[18]

Determining ADPKD disease progression requires more than monitoring kidney function alone[19]

Irreversible kidney damage has already occurred by the time GFR begins to decline[3,19,20]

Asymptomatic for years

Patients with ADPKD may remain asymptomatic for years while the disease progresses, likely due to compensatory hyperfiltration[19,21]

Normal lab results

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[3,22]

Enlarged kidneys

While eGFR remains stable, kidney volume can grow 4-6 times greater than normal and irreversible kidney damage has occurred[23]

Loss of kidney function

By the time adult patients reach CKD Stage 3, their eGFR has significantly declined and 50% of kidney function is lost[22]

Patients presenting with a rapid decline in eGFR are already experiencing rapid disease progression[2,20*]

*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.[2]

Identify risk factors associated with risk of rapid progression

If a patient presents with any of these independently validated risk factors, they could be appropriate for treatment[8]

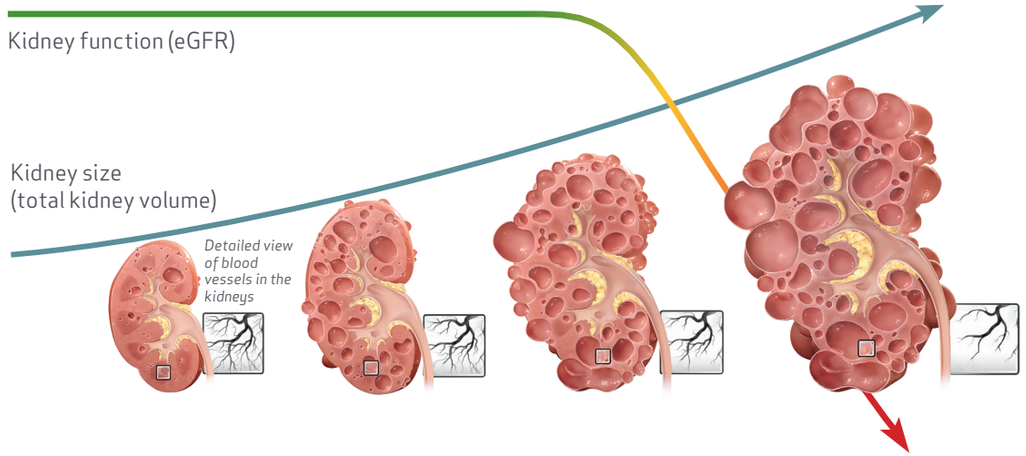
TKV greater than expected for age[11,12]

Kidney size has been shown to be a strong predictor of the rate of ADPKD progression[4]

- **Overweight and obesity (BMI ≥25 kg/m^2)[9]**
- **Family history of ESKD at or before age 58[2]**
- **Hypertension before age 35[10]**
- **Urologic events before age 35[10]** (gross hematuria, cyst infection, or flank pain related to cysts)
- **Proteinuria and microalbuminuria[8]**
- **Truncating *PKD1* mutation[10]**

Kidney size is a strong predictor of ADPKD progression[4]

In ADPKD, kidney growth and damage often occur before kidney function declines[3,19]



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

- **Progression of ADPKD** can often go **unnoticed**. Normal kidney function can mask the severity of disease progression until **irreversible damage has already occurred**[19]
- In most patients with ADPKD, eGFR levels do not decline until they are **40 or 50** years old, when **kidneys are grossly enlarged**[17]

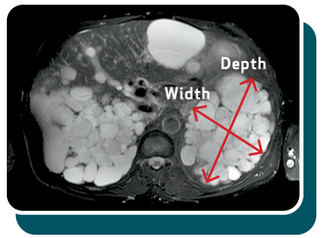
A CRISP cohort analysis, published in *Kidney International*, showed that a one-time measurement of TKV can help assess the rate of future kidney function decline[24]

NIH=National Institutes of Health.

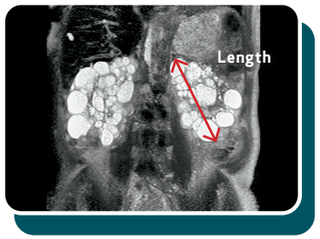
The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) is an NIH-funded, 14-year observational study (N=241) of adult ADPKD patients. The primary goal was to determine the extent to which TKV forecasts the development of renal insufficiency in ADPKD.[24,25]

There are multiple ways to measure kidney size

Total kidney volume



MRI/CT



MRI or CT scan can reliably measure kidney size to calculate TKV[6,7]

- Identifying a TKV greater than expected for patient's age can provide an early and reliable marker for rapid disease progression and predict future kidney function decline[11,12]
- TKV can be assessed using ultrasound, but it lacks precision and accuracy and is highly operator dependent[6]

Utilize the ellipsoid formula to calculate TKV[6,11]

1. Request kidney length, width, and depth measurements
2. Calculate TKV using the ellipsoid formula

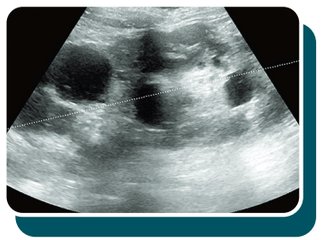
   $\frac{\pi}{6} \bullet (L \times W \times D) = TKV$

3. Calculate htTKV using the patient's height and TKV

   $\frac{TKV\ (mL)}{height\ (m)} = htTKV\ (mL/m)$

4. Determine ADPKD imaging classification using the Mayo Imaging Classification tool to assess risk of rapid progression[6]

Kidney length



Ultrasound

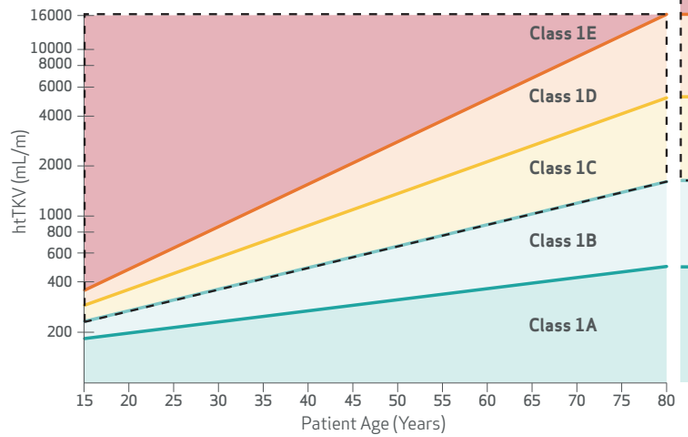
In younger patients, ultrasound kidney length can be used when MRI/CT-calculated TKV is not available[2,6]

- Based on the CRISP study, ultrasound kidney length >16.5 cm in patients aged <45 years can indicate a risk of rapid progression[2,6]
  - —In the CRISP study, a kidney length of >16.5 cm was shown to predict development of CKD Stage 3 within 8 years in patients with ADPKD who were <45 years of age and who had CKD Stage 1 or 2[4*]

*Average baseline GFR of 98 mL/min/1.73 m^2.[4]

Identifying a TKV greater than expected for a patient's age can provide an early and reliable marker for rapid disease progression in ADPKD[11,12]

The Mayo Imaging Classification is a simple tool using htTKV and age to identify a patient's risk of ADPKD progression[6,7†]



Estimated kidney growth rate: yearly percentage increase	Estimated slope of change in eGFR	Risk for eGFR decline
>6.0%	-4.78	High risk
4.5% – 6.0%	-3.48	High risk
3.0% – 4.5%	-2.63	High risk
1.5% – 3.0%	-1.33	Intermediate risk
<1.5%	-0.23	Low risk

eGFR units=mL/min/1.73 m^2/yr.

Republished with permission of The American Society of Nephrology, from Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol*. 2015;26(1):160-172.

- Patients with ADPKD in Class 1C, 1D, and 1E are at risk of future rapid kidney function decline and could be candidates for treatment[7]

~2/3 of the ADPKD patients evaluated in the Mayo Clinic ADPKD imaging classification study were identified as being at risk of rapid progression[7‡]

†Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV. Classification only applies to patients with typical morphology of ADPKD as defined by diffuse bilateral cystic involvement of the kidneys.[7]

‡357 of the 538 patients in this study were identified as being at risk of rapid progression (1C-1E).[7]

REPRISE—A 12-month trial of patients with CKD late Stage 2 to early Stage 4

REPRISE=Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy.

Trial phases[26]

STUDY DESIGN

- Phase 3, double-blind, placebo-controlled withdrawal trial
- 1370 patients randomized 1:1 to treatment with JYNARQUE or placebo
  - 18 to 55 years of age: eGFR between 25 and 65 mL/min/1.73 m^2
  - 56 to 65 years of age: eGFR between 25 and 44 mL/min/1.73 m^2 plus eGFR decline >2.0 mL/min/1.73 m^2/year
- During the titration period, patients were up-titrated every 3 to 4 days with JYNARQUE
  - 30 mg AM + 15 mg PM/day
  - 45 mg AM + 15 mg PM/day
  - 60 mg AM + 30 mg PM/day
  - 90 mg AM + 30 mg PM/day
- Only patients who could tolerate the 2 highest doses of JYNARQUE (60 mg/30 mg or 90 mg/30 mg) were randomized 1:1 to treatment with JYNARQUE or placebo; during the 12-month study, they could interrupt, decrease, and/or increase the dose as clinical circumstances warranted
- **Primary endpoint: the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized by dividing by each participant's treatment duration**

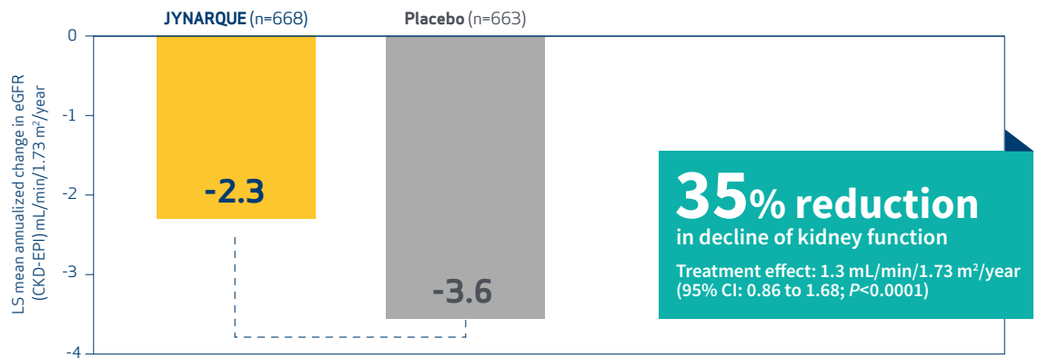
SELECT IMPORTANT SAFETY INFORMATION:

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.

Please see **IMPORTANT SAFETY INFORMATION** on pages 24-25.

JYNARQUE® (tolvaptan) significantly reduced the decline in kidney function

Change in eGFR from pre-treatment baseline to post-treatment follow-up over 12 months[27]



CI=confidence interval; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; LS=least squares.

SELECT IMPORTANT SAFETY INFORMATION:

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.

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TEMPO 3:4—A 36-month trial in patients with CKD stages 1, 2, and 3

TEMPO=Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

TEMPO 3:4 trial phases[14,28]

STUDY DESIGN[14]

- 1445 patients randomized 2:1 to treatment with JYNARQUE or placebo
  - 18 to 50 years of age
  - Early, rapidly progressing ADPKD (meeting modified Ravine criteria*)
  - TKV ≥750 mL
  - Creatinine clearance ≥60 mL/min
- Patients were up-titrated weekly with JYNARQUE or placebo doses studied:
  - 45 mg AM + 15 mg PM/day
  - 60 mg AM + 30 mg PM/day
  - 90 mg AM + 30 mg PM/day
- Patients were to maintain the highest tolerated dose for 3 years
- **Primary endpoint: annual rate of change in the total kidney volume**

TEMPO 4:4 EXTENSION TRIAL[29]

A multicenter, open-label, extension trial provided an additional 2 years of data on the long-term safety and efficacy of JYNARQUE in patients completing TEMPO 3:4.

SELECT IMPORTANT SAFETY INFORMATION:

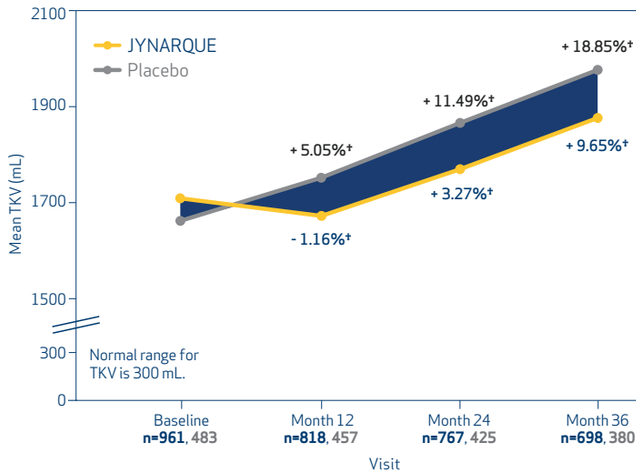
Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP3A inhibitors is contraindicated; dose reduction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

*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.[30,31]

Please see **IMPORTANT SAFETY INFORMATION** on pages 24-25.

JYNARQUE® (tolvaptan) slowed TKV growth

Change in TKV from baseline normalized as a percentage[32]



49% reduction
at the end of 3 years‡ (*P*<0.001)
Month 36 treatment effect: -9.2%

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 on kidney size beyond what accrued during the first year of treatment.§

KEY SECONDARY COMPOSITE ENDPOINT

JYNARQUE decreased the relative rate of ADPKD-related composite events by 13.5%‖

The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of[14]**:**

COMPONENT 1	COMPONENT 2	COMPONENT 3	COMPONENT 4
Worsening kidney function	**Medically significant kidney pain**	**Worsening hypertension**	**Worsening albuminuria**

The results were driven by effects on worsening kidney function and kidney pain events. In contrast, tolvaptan had no effect on progression of either hypertension or albuminuria.

To learn more about the secondary endpoint results evaluated in TEMPO 3:4, visit JYNARQUEhcp.com

SELECT IMPORTANT SAFETY INFORMATION:

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.

†Percent change from baseline.

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

§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.[32]

‖44 versus 50 events per 100 person-years of follow-up. HR, 0.87; 95% CI, 0.78 to 0.97; *P*=0.0095.

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Clinical safety profile of JYNARQUE® (tolvaptan)

The safety profile of JYNARQUE has been evaluated in more than 2800 patients across CKD stages 1-4, in the 2 largest clinical trials of patients with ADPKD[14,33,34]

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; ULN=upper limit of normal.
*Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria.
†Thirst includes polydipsia and thirst.

Please see **IMPORTANT SAFETY INFORMATION** on pages 24-25.

Discontinuation rates with JYNARQUE® (tolvaptan)

Discontinuations due to adverse events were 15% (n=148/961) for patients taking JYNARQUE vs 5% (n=24/483) taking placebo

Post-hoc analysis of discontinuations due to aquaretic adverse events (AAEs) in TEMPO 3:4[35]

- In total, 750 of 961 (78%) of patients treated with JYNARQUE reported an AAE; 72 (10%) patients discontinued because of an AAE, and 573 (76%) continued treatment[35]
- AAEs were most pronounced shortly after initiation of JYNARQUE, with tolerability appearing to stabilize by the month 4 visit[35]
- ADPKD patients at earlier stages of disease progression may be more sensitive to aquaretic symptoms, which might influence tolvaptan dosing and titration decisions for the future[35]
- The median time to discontinuation due to an AAE was 96 days (overall range: 2-877 days)[35]

SELECT IMPORTANT SAFETY INFORMATION:

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.

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Risk of serious liver injury with JYNARQUE® (tolvaptan)

- **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**

- **In a 3-year placebo-controlled trial and its open-label extension (in which patients' liver tests were monitored every 4 months), evidence of serious hepatocellular injury (elevations of hepatic transaminases of at least 3 times ULN combined with elevated bilirubin at least 2 times the ULN) occurred in 0.2% (3/1487) of tolvaptan treated patients compared to none of the placebo treated patients**

- **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**

- **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 48-72 hours), 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 3 times ULN**

- **Do not restart JYNARQUE in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times 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 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring**

Please see **IMPORTANT SAFETY INFORMATION** on pages 24-25.

Due to the risk of serious liver injury, JYNARQUE® (tolvaptan) is available only through the REMS Program

The JYNARQUE REMS Program makes monitoring your patients and mitigating the risk of liver injury a top priority

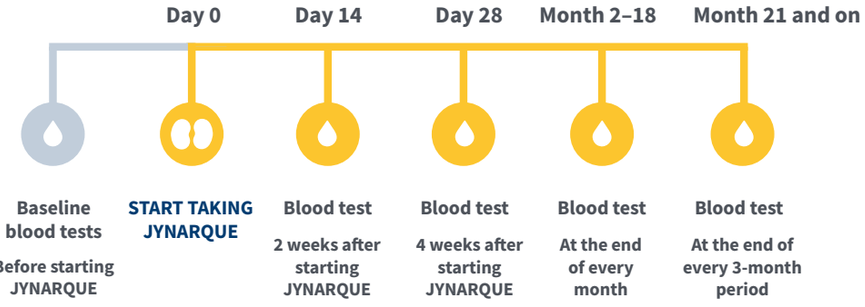
- **0.2% (3/1487)** of JYNARQUE patients experienced serious hepatocellular injury in a 3-year placebo-controlled trial and its open-label extension (in which patients' liver tests were monitored every 4 months) compared to none of the placebo-treated patients*
- In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (**4.9% [80/1637] versus 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

Enrollment takes just minutes† and ongoing support is available

- Become enrolled by completing a one-time certification process
- JYNARQUE is only available through specialty pharmacies which deliver medication directly to patients. In addition to delivering the prescription, they also provide educational support tailored to your needs

*Elevations of hepatic transaminases of at least 3 times ULN combined with elevated bilirubin at least 2 times ULN.
†Individual times may vary.

Ongoing regular blood tests will help monitor patients' hepatic enzymes and mitigate risk



- Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, monthly for 18 months, and every 3 months thereafter during treatment with JYNARQUE

AST=aspartate aminotransferase; REMS=Risk Evaluation and Mitigation Strategy.

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Dosing and administration of JYNARQUE® (tolvaptan)

Patients should be advised to take JYNARQUE twice daily, the first dose upon waking and the second dose 8 hours later

	Immediately upon waking		8 hours later		Total daily dose
INITIAL DOSE	45 mg	+	15 mg	=	60 mg
TITRATION STEP	60 mg	+	30 mg	=	90 mg
TARGET DOSE	90 mg	+	30 mg	=	120 mg

The pill shape and color are graphical representations and are not actual size.

- Titrate to 60 mg + 30 mg, then to 90 mg + 30 mg per day if tolerated, with at least weekly intervals between titrations
- Encourage patients to drink enough water to avoid thirst or dehydration
- Patients may down-titrate based on tolerability
- If a dose of JYNARQUE is not taken at the scheduled time, take the next dose at its scheduled time

SELECT IMPORTANT SAFETY INFORMATION:

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

Please see **IMPORTANT SAFETY INFORMATION** on pages 24-25.

Otsuka is committed to making JYNARQUE® (tolvaptan) affordable and available

Eligible commercially insured patients pay as little as **$10 per month for JYNARQUE.***

>96% of patients with commercial insurance have coverage for JYNARQUE.[36]

JYNARQUE is available through limited distribution pharmacies

alliance**Rx** Walgreens Pharmacy	Optum	PANTHERRARE
aliancerxwp.com	optum.com	pantherxrare.com
800-480-9052	877-719-6330	833-599-2245

Specialty pharmacies can:

- Mail medication directly to patients
- Offer clinical and educational support by nurses and pharmacists
- Provide lab tests and refill reminders
- Coordinate with patients and prescribers

*Assumes one 28-day supply prescription per month. If more than one prescription is filled in a calendar month, patient may pay more than $10 in that month. Offer is not transferable. Patients are not eligible if they are under 18 years of age, or are covered in whole or in part by any state program or federal healthcare program, including but not limited to, Medicare or Medicaid (including Medicaid managed care), Medigap, VA, DOD, or TRICARE. Only valid in US and Puerto Rico. Offer void where prohibited by law, taxed or restricted. Other restrictions may apply. This program is not health insurance. Otsuka America Pharmaceutical, Inc. has the right to rescind, revoke or amend this program at any time without notice. Your participation in this program confirms that this offer is consistent with your insurance coverage and that you will report the value received if required by your insurance provider. When you use this program, you are certifying that you understand and comply with the program rules, terms and conditions.

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

At Otsuka, we are committed to providing resources and tools for your patients

Once you have determined that JYNARQUE® (tolvaptan) is the appropriate treatment for your patients, there are resources and tools for your patients to facilitate REMS compliance and more.

Peer Mentor Program—Your patients can speak with a Peer Mentor to hear their story about living with rapidly progressing ADPKD and their experience taking JYNARQUE.

Topics may include:

- Daily life with ADPKD
- ADPKD treatment and the workplace
- ADPKD symptoms
- Treatment with JYNARQUE
- Patient support services for JYNARQUE
- Side effects of JYNARQUE
- Communicating with family and friends
- JYNARQUE REMS safety program

To register or for more information about the ADPKD Peer Mentor Program, call 855-415-7459 or visit adpkdpeermentorprogram.com.

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 24-25.

Help your patients start and continue JYNARQUE® (tolvaptan) using counseling tips provided by your peers

As part of patient counseling, review the JYNARQUE Medication Guide with every patient

Starting Treatment

- Advise your patients to **drink enough water** to avoid thirst and dehydration[37]
- Consider starting JYNARQUE on a **weekend**, or when patients are **not at work**[37]
- Advise patients that **titration is based on tolerability**—lifestyle and daily activities should be taken into account

Taking JYNARQUE[37-39]

- Offering **dietary counseling** may help patients tolerate the aquaretic side effects of JYNARQUE
- Decreasing a patient's **protein and sodium** intake may help reduce urine volume
- Advise patients that taking the **first dose upon waking** and **second dose 8 hours later** can help **reduce the need to wake up to use the bathroom at night**

Getting Ready for Shipment

- JYNARQUE will be shipped to your patients each month from their **specialty pharmacy**
- Your patients will need to provide **shipping and copay details** to the specialty pharmacy to avoid delays with their shipment
- Help your patients adhere to their REMS-required testing by providing **reminders and a copy of the test schedule**

Helpful Reminders

- Suggest using the **restroom before** meetings, movies, travel, and social events
- Suggest that patients **set alarms or reminders** for each dose of JYNARQUE
- Encourage patients to **set a recurring calendar event** for lab testing and other appointments
- Mobile apps like SitOrSquat, Flush, or Toilet Finder can help patients locate nearby restrooms while away from home*

Join over 4000 physicians who have already prescribed JYNARQUE in their commitment to helping their patients with ADPKD[40]

*Otsuka does not control or influence any of these apps.

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Find patients appropriate for JYNARQUE® (tolvaptan)

Take a look at some appropriate patient types.
(Patient images and patient cases are fictional.)

Bob, 53—Stage 3A CKD

Bob's rapidly declining eGFR is evidence of rapidly progressing ADPKD

His nephrologist noticed a decrease in eGFR of 5 mL/min/1.73 m^2 over a 1-year period—evidence of rapidly progressing ADPKD.

After further assessment, his nephrologist determined Bob was an appropriate patient and recommended he start treatment with JYNARQUE.

Tim, 31—Stage 2 CKD

Even though Tim had a relatively stable eGFR, his family history of early ESKD led his nephrologist to scan his kidneys for a TKV measurement.

His nephrologist knew that CRISP data show that a one-time measurement of TKV can help assess the rate of progression and predict the rate of future kidney function decline.*

Given the Mayo Imaging Classification of 1C, Tim's nephrologist determined he was at high risk for rapidly progressing ADPKD.

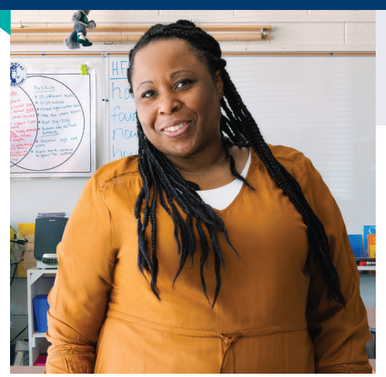
After further assessment, Tim's nephrologist determined he was an appropriate patient and recommended he start treatment with JYNARQUE.

SELECT IMPORTANT SAFETY INFORMATION:

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.

Please see **IMPORTANT SAFETY INFORMATION** on pages 24-25.

Julia, 40—Stage 2 CKD



Julia's many risk factors, including obesity, proteinuria, and hypertension before age 35, led her nephrologist to request an ultrasound to determine her kidney length.

Because her kidney length was greater than 17 cm at 40 years of age with CKD Stage 2, Julia's nephrologist determined that she was at risk for rapidly progressing ADPKD.

After further assessment, Julia's nephrologist determined she was an appropriate patient and recommended she start treatment with JYNARQUE.

*The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) is an NIH-funded, 14-year observational study (N=241) of adult ADPKD patients. The primary goal was to determine the extent to which TKV forecasts the development of renal insufficiency in ADPKD.[24,25]

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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**.

For your adult patients at risk of rapidly progressing ADPKD,

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

S — **Slow decline of kidney function**
JYNARQUE is the first and only FDA-approved treatment indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD

T — **Two largest ADPKD trials**[14,33,34]
Across a spectrum of CKD stages

A — **Assess kidney size**[3,19,24,41]
A strong predictor of the rate of ADPKD progression

R — **REMS and patient support**
Otsuka partners with you to monitor your patients and help mitigate the risk of serious liver injury

T — **Ten dollars per month ($10)**
Eligible commercially insured patients pay as little as $10 per month for JYNARQUE*

To see the type of patients who may be appropriate for JYNARQUE, visit JYNARQUEhcp.com

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 24-25.

CKD=chronic kidney disease; REMS=Risk Evaluation and Mitigation Strategy.

*Assumes one 28-day supply prescription per month. If more than one prescription is filled in a calendar month, patients may pay more than $10 in that month. Other terms and conditions may apply.

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October 2022 10US22EBP0172