Patient counseling is a cornerstone of treatment with JYNARQUE® (tolvaptan)

It's important to set expectations for your patients taking JYNARQUE, so they know what to expect from treatment and can stay motivated.

Featuring Dr Gerard J Tepedino
PRINE Health Medical Group, PLLC, Manhasset, New York

INDICATION:

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

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 Tolvaptan for ADPKD Shared System REMS**

Please see **IMPORTANT SAFETY INFORMATION** on pages 16 and 17.

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

Confidently prepare your ADPKD patients for treatment

This educational guide will help give you a better understanding of JYNARQUE® (tolvaptan) so you can let your patients know what they can expect throughout their treatment journey.

Your patients may have questions before starting treatment with JYNARQUE.

Working closely with your patients and setting expectations can help motivate them to stay on track throughout treatment.

Dr Gerard J Tepedino, a clinical nephrologist in practice since 2005, shares his insights and his experiences preparing appropriate patients for treatment with JYNARQUE.

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

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

ADPKD=autosomal dominant polycystic kidney disease.

Please see **IMPORTANT SAFETY INFORMATION** on pages 16 and 17.

> If the patient is invested in the decision to start treatment from the beginning, I find it is more likely that they will be able to stay motivated throughout the course of treatment.

Dr Tepedino served as a staff physician for several years at The Rogosin Institute in New York City.

Dr Tepedino received his MD from New York University Grossman School of Medicine in New York City, subsequently completing his residency in internal medicine at New York University Medical Center, Bellevue Hospital.

He completed a fellowship in nephrology at New York-Presbyterian Hospital/Weill Cornell Medical Center in 2005, and is board certified in internal medicine and nephrology.

Dr Tepedino is a paid consultant of Otsuka America Pharmaceutical, Inc.

Clinical Trial Results

Your patients may have questions about the benefits of JYNARQUE® (tolvaptan)

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD. As a disease-modifying treatment, JYNARQUE can decrease the rate of cyst growth.[1]

When you speak to your patient, you can explain that JYNARQUE has been studied across a spectrum of CKD stages, from Stage 1 through Stage 4. I also make sure to highlight to my patients that JYNARQUE is for people at risk of rapidly progressing ADPKD.

Highlight the efficacy results reported in the 2 largest clinical trials of JYNARQUE® (tolvaptan), studied in over 2800 patients across a spectrum of CKD stages[2-4]

REPRISE clinical trial: a 12-month study of patients with CKD late Stage 2 to early Stage 4[4,5]

- **35% reduction in the 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)

Study design: 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.[4,6]**

TEMPO 3:4 clinical trial: a 36-month study of patients with CKD Stages 1, 2, and 3[3,7]

- **49% reduction of TKV growth vs placebo 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.†

Study design: 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 TKV.[3]**

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.

CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; REPRISE=Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy; TEMPO=Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV=total kidney volume.

*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.[8,9]

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Clinical Safety Profile

Your patients may have questions about the 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 with ADPKD.[2-4]

“When discussing with patients the most common side effects observed in trials, I make sure they understand that aquaretic adverse events, including increased urination and thirst, are related to how JYNARQUE acts in the kidneys.”

Review the clinical safety profile of JYNARQUE® (tolvaptan) with your patients to help set expectations for potential adverse reactions

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

Discontinuations due to an adverse event were 15% (n=148) for patients taking JYNARQUE vs 5% (n=24) taking placebo.

*Increased urination includes micturition urgency, nocturia, pollakiuria, and polyuria.

†Thirst includes polydipsia and thirst.

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

Your patients may have concerns about taking JYNARQUE® (tolvaptan) due to the risks of liver injury.

Due to the risks of liver injury, JYNARQUE is available only through a Tolvaptan for ADPKD Shared System REMS, which makes monitoring your patients to help mitigate the risk of liver injury a top priority.

“It’s helpful to explain that the purpose behind the Tolvaptan for ADPKD Shared System REMS is to help reduce the risk of liver injury in people taking JYNARQUE. I find that if I explain this to my patients, they are more accepting of participating in the program.”

The REMS Program is in place to monitor your patients to help mitigate the risks of liver injury. It’s important to properly contextualize the incidence of liver injury as seen in the clinical trials

In clinical trials:

Incidence of serious liver injury

- **0.2% (3/1487)** of JYNARQUE® (tolvaptan) patients experienced serious hepatocellular injury (elevations of hepatic transaminases of at least 3 times ULN combined with elevated bilirubin at least 2 times the ULN) 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

Incidence of liver injury

- **4.9% (80/1637)** of JYNARQUE patients experienced ALT elevations >3 times the ULN at an increased frequency within the first 18 months after initiating treatment compared to 1.1% (13/1166) of patients taking placebo in the two double-blind, placebo-controlled trials. **ALT elevations usually resolved within 1 to 4 months after discontinuing treatment**

Advise patients to stop taking JYNARQUE and notify their HCP if they show signs or symptoms of liver injury.

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 their needs

Ongoing regular blood tests to monitor patients’ hepatic enzymes and help mitigate risk

- **Complete the baseline liver testing before initiating the first dose, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months, and every 3 months thereafter**
- **Your patients must enroll in the Tolvaptan for ADPKD Shared System REMS and comply with these monitoring requirements**

ALT=alanine transaminase; REMS=Risk Evaluation and Mitigation Strategy; ULN=upper limits of normal.

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Aquaretic Adverse Events (AAEs)

Your patients may have concerns about how much water they will need to drink and how frequently they may have to urinate

Dietary and lifestyle management tips can help reduce the aquaretic effect of JYNARQUE® (tolvaptan).[10]

> If we are able to help make the connection in the patient's mind between how the medicine works and why they are urinating and drinking so much water, I think psychologically it may be easier for them to tolerate side effects and adapt their lifestyle.

It is important to set expectations with your patients and offer them practical tips for managing AAEs throughout the course of treatment

First, you could mention that the onset of AAEs are related to the mechanism of action of JYNARQUE® (tolvaptan)

- JYNARQUE targets vasopressin, a hormone that maintains the volume of water in the fluid space surrounding the cells; people with ADPKD have too much vasopressin, causing kidney cysts to grow
- JYNARQUE works by selectively inhibiting the binding of vasopressin at the V_2-receptor in the kidney

Post-hoc analysis of discontinuations due to AAEs in TEMPO 3:4[11]

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

These peer-reviewed tips can help patients manage AAEs:

- Reducing sodium and protein intake may help reduce urine volume[10]
- Take a water bottle everywhere you go to stay hydrated, and try to stay away from drinks with high sugar content
- Plan ahead to find the restrooms near where you'll be
- Take the first JYNARQUE dose upon waking and the second dose exactly 8 hours later, and you may be able to reduce the need to wake up to urinate[10]

Please see **IMPORTANT SAFETY INFORMATION** on pages 16 and 17.

Resources and Tips

Your patients may have questions about starting treatment with JYNARQUE® (tolvaptan)

There are resources, like the Medication Guide, and tips from your peers available to help you support your patients throughout their treatment journey.

> We generally want to communicate the need for exercise and general health to make sure that patients are in as good of shape as possible.

Use the peer-provided counseling tips to help your patients start and continue JYNARQUE® (tolvaptan)

Tips for starting JYNARQUE[10]

- Prior to starting treatment, consider advising your patients to increase their normal water intake
- Recommend that your patients start JYNARQUE on a weekend, or when they are not at work
- Take into account patients' individual lifestyle and daily activities when assessing the dosing and titration of JYNARQUE
- Offering dietary counseling may help patients tolerate the aquaretic side effects of JYNARQUE
- The tone you use to present treatment information really matters to your patients and will affect how they view their treatment

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

Helpful reminders for patients

- 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 restroom finder apps can help patients locate restrooms while away from home
- Sharing experiences with their family, friends, and healthcare team can help patients feel more comfortable with treatment; being open about their condition is crucial to managing the emotional impact

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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Resources and Tips

Your patients might want to hear from someone already taking JYNARQUE® (tolvaptan) before starting treatment

Otsuka is committed to supporting your patients with ADPKD by offering programs that allow them to hear first-hand accounts from real patients taking JYNARQUE.

Encouraging patients to share experiences with family, friends, and their healthcare team can make them feel more comfortable with treatment.

Your patients may benefit from speaking with a Peer Mentor to hear their story about living with ADPKD and their experiences taking JYNARQUE® (tolvaptan)

Peer Mentor Program topics 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
- Tolvaptan for ADPKD Shared System REMS

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

Meet Gen J

Hear from the first generation of patients at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) with a treatment to call their own. Watch their videos and read their stories for a closer look into their experiences with ADPKD and their treatment journeys.

Visit JYNARQUE.com/patient-stories.

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

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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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 Tolvaptan for ADPKD Shared System REMS**

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 for JYNARQUE® (tolvaptan) (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**.

Patient counseling is a cornerstone of treatment with JYNARQUE® (tolvaptan)

Building a strong relationship with your patients and setting expectations can help them become more comfortable with starting JYNARQUE, and can keep them motivated to stay on the course of treatment.

To learn more about treatment, patient counseling, and setting expectations, visit JYNARQUEhcp.com.

If you have any questions, reach out to your local representative or call the Otsuka Connect Call Center at 1-833-4-OTSUKA (1-833-468-7852).

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References: 1. Chebib FT, Torres VE. *Am J Kidney Dis*. 2021;78(2):282-292. **2.** Data on file. TOLV-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **3.** Torres VE, Chapman AB, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *N Engl J Med*. 2012;367(25):2407-2418. **4.** Torres VE, Chapman AB, Devuyst O, et al; for the REPRISE Trial Investigators. *N Engl J Med*. 2017;377(20):1930-1942. **5.** Data on file. JYN-012. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **6.** Torres VE, Devuyst O, Chapman AB, et al. *Am J Nephrol*. 2017;45(3):257-266. **7.** Torres VE, Meijer E, Bae KT, et al. *Am J Kidney Dis*. 2011;57(5):692-699. **8.** Belibi FA, Edelstein CL. *J Am Soc Nephrol*. 2009;20(1):6-8. **9.** Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM. *Lancet*. 1994;343(8901):824-827. **10.** Chebib FT, Perrone RD, Chapman AB, et al. *J Am Soc Nephrol*. 2018;29(10):2458-2470. **11.** Devuyst O, Chapman AB, Shoaf SE, et al. *Kidney Int Rep*. 2017;2(6):1132-1140.

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