TAKE A STAND AGAINST ADPKD

JYNARQUE is the first and only FDA-approved treatment indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

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

SELECT 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**

Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

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

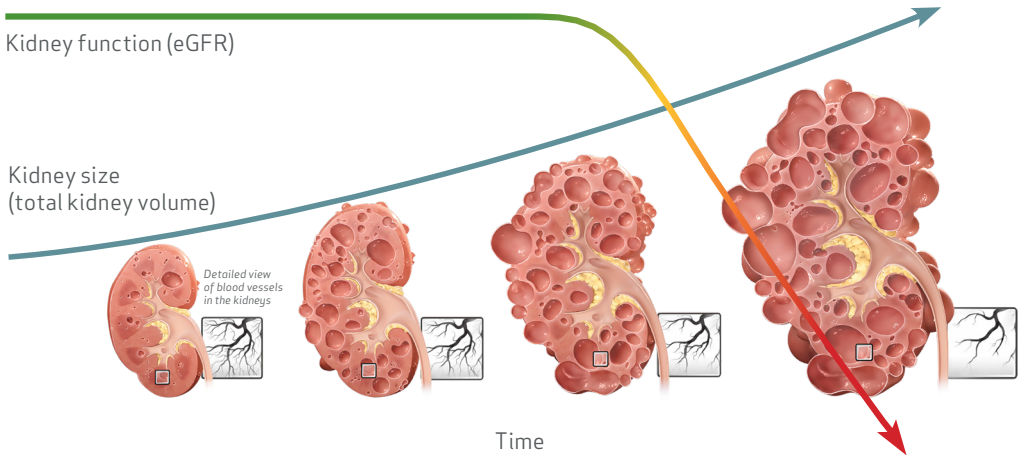
What is autosomal dominant polycystic kidney disease (ADPKD)?

- ADPKD is a genetic, progressive disease that is characterized by the continuous development and enlargement of cysts in the kidneys[1,2]
- ADPKD is the most common life-threatening genetic disease and the 4th leading cause of end-stage kidney disease (ESKD)[3,4]

Assessing kidney size can help predict rate of future kidney function decline[5,6]

- Patients with ADPKD may remain asymptomatic for years while the disease progresses, likely due to compensatory hyperfiltration[5,7]
- The rate of progression in ADPKD is variable from patient to patient[3,8]

MEASURING KIDNEY FUNCTION ALONE MAY NOT REVEAL HOW ADPKD IS PROGRESSING[5,9,10]



Changes in kidney size often precede kidney function decline

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

eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease.

Nearly 50% of patients with ADPKD will reach ESKD by age 60[11]

Early identification of patients who are at risk for rapid progression may provide an opportunity for intervention

RISK FACTORS ASSOCIATED WITH RAPID DISEASE PROGRESSION*

Kidney size greater than expected for age[12,13]

eGFR decline[16]**:**
≥5 mL/min/1.73 m^2 within 1 year

OR

≥2.5 mL/min/1.73 m^2 per year over ≥5 years

Truncating *PKD1* mutation[14,15]

Family history of ESKD at or before age 58[16]

Urologic events before age 35[14]

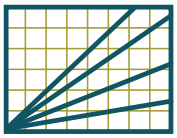
- Gross hematuria
- Cyst infection
- Flank pain related to cysts

Hypertension before age 35[14,15]

*Male gender has been identified as an additional risk factor.[15,17]

It's important to look beyond eGFR when determining if your patients are at risk of rapidly progressing ADPKD[5]

Imaging modalities can help assess kidney size to identify patients at risk of rapid progression[18,19]

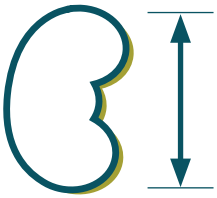


Order an MRI or CT scan to reliably measure kidney size[12,18]

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

   $\frac{TKV}{\text{height (m)}} = \text{htTKV}$
4. **Determine ADPKD Imaging Classification** using the Mayo Imaging Classification tool to assess risk of rapid progression



Ultrasound kidney length when MRI/CT-calculated TKV is not available

Based on the CRISP study, ultrasound kidney length >16.5 cm in patients aged <45 years can indicate a risk of rapid progression[16,18]*

- In the CRISP study, ADPKD patients <45 years of age with CKD Stage 1 or 2,† a kidney length >16.5 cm has been shown to predict future development of CKD Stage 3a within 8 years[20]

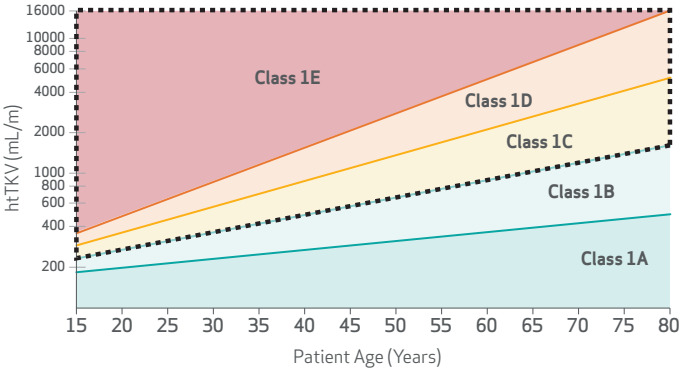
CKD=chronic kidney disease; CRISP=Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; CT=computed tomography; GFR=glomerular filtration rate; htTKV=height-adjusted total kidney volume; MRI=magnetic resonance imaging; TKV=total kidney volume.
*A direct measurement of TKV would be required if a more accurate assessment is needed.
†Average baseline GFR of 98 mL/min/1.73 m^2.

A CRISP cohort analysis, published in *Kidney International*, shows that a one-time measurement of TKV can help predict future kidney function decline[21]

Assessing patients at risk of rapid progression

ADPKD imaging classification by htTKV and age predicts the change in eGFR over time[19‡]

MAYO CLINIC IMAGING CLASSIFICATION OF ADPKD[18,19]



PATIENT CLASSIFICATION§

Class	Est. kidney growth rate: yearly percentage increase	Estimated slope of change in eGFR	Risk for eGFR decline
1E	>6.0%	-4.78	High risk
1D	4.5% –6.0%	-3.48	High risk
1C	3.0% – 4.5%	-2.63	High risk
1B	1.5% – 3.0%	-1.33	Intermediate risk
1A	<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.

‡Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV.[19]

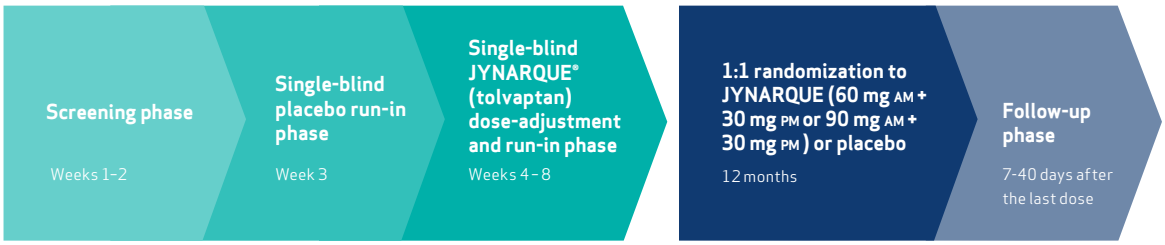
§Classification applies only to patients with typical morphology of ADPKD as defined by diffuse bilateral cystic involvement of the kidneys.[19]

~2/3 of the ADPKD patients evaluated in the Mayo Clinic ADPKD imaging classification study were identified to be at risk of rapid progression[19]

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[22]



8-week prerandomization period

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 end point: the treatment difference in the change of eGFR from pretreatment baseline to posttreatment follow-up, annualized by dividing by each participant's treatment duration**

SELECT IMPORTANT SAFETY INFORMATION:

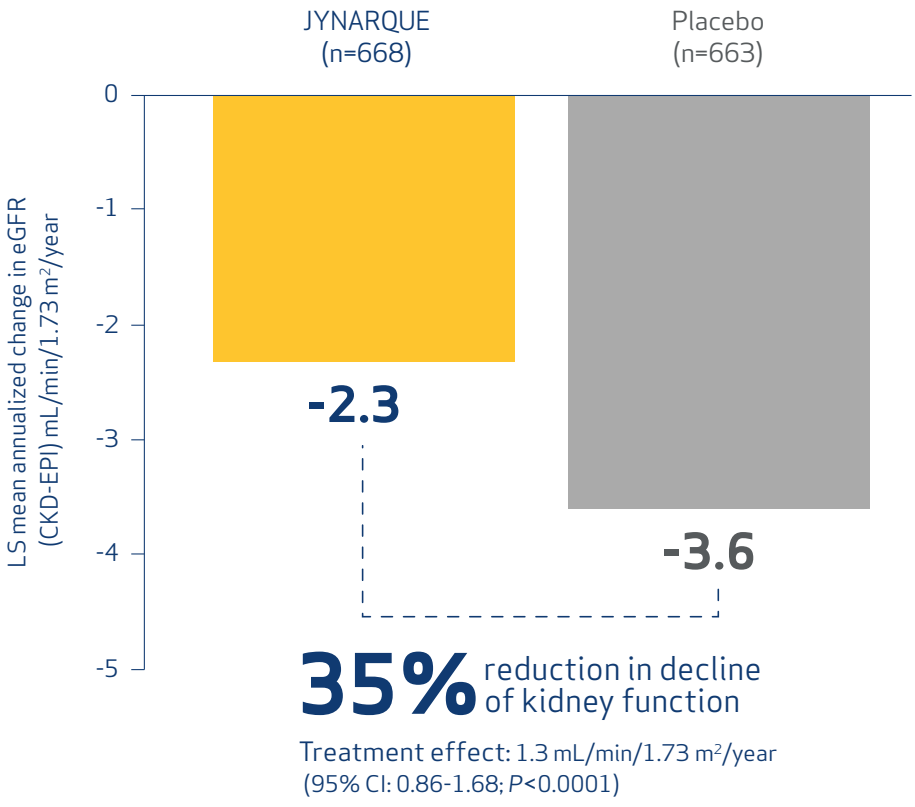
CONTRAINDICATIONS:

- 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 18-19.

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

CHANGE IN eGFR FROM PRETREATMENT BASELINE TO POSTTREATMENT FOLLOW-UP OVER 12 MONTHS[23]



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.

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

Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

JYNARQUE® (tolvaptan)
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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.

TRIAL PHASES [2,24]

STUDY DESIGN[2]

- Phase 3, double-blind, placebo-controlled trial
- 1445 patients randomized 2:1 to treatment with JYNARQUE® (tolvaptan) 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 end point: difference for rate of change of TKV normalized as a percentage**

TEMPO 4:4 EXTENSION TRIAL[25]

- 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:

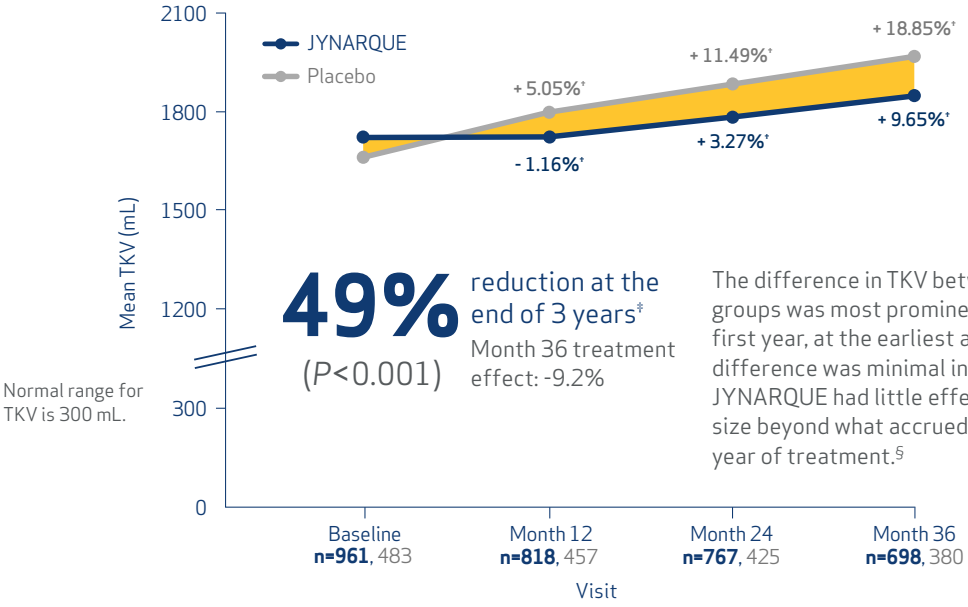
Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because 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.

*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.[26,27]

Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

JYNARQUE® (tolvaptan) slowed TKV growth

CHANGE IN TKV FROM BASELINE NORMALIZED AS A PERCENTAGE[28]



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 END POINT

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

The key secondary composite end point (ADPKD progression) was time to multiple clinical progression events of:

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

Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

JYNARQUE® (tolvaptan)
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Clinical safety profile of JYNARQUE® (tolvaptan)

TEMPO 3:4—Treatment-emergent adverse reactions in ≥3% of JYNARQUE-treated patients with risk difference ≥1.5%, randomized period

	Percentage of patients reporting reaction	
Adverse 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] 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.

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 18-19.

Discontinuation rates with JYNARQUE® (tolvaptan)

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

Post-hoc analysis of discontinuations due to aquaretic adverse events (AAEs) in TEMPO 3:4[29]

- In total, 750 of 961 (78%) of patients treated with JYNARQUE reported an AAE; 72 (10%) of patients discontinued because of an AAE, and 573 (76%) continued treatment
- The median time to discontinuation due to an AAE was 96 days (overall range: 2-877 days)
- AAEs were most pronounced shortly after initiation of JYNARQUE, with tolerability appearing to stabilize by the month 4 visit
- 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

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.

Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

Risk of 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**

AST =aspartate aminotransferase.

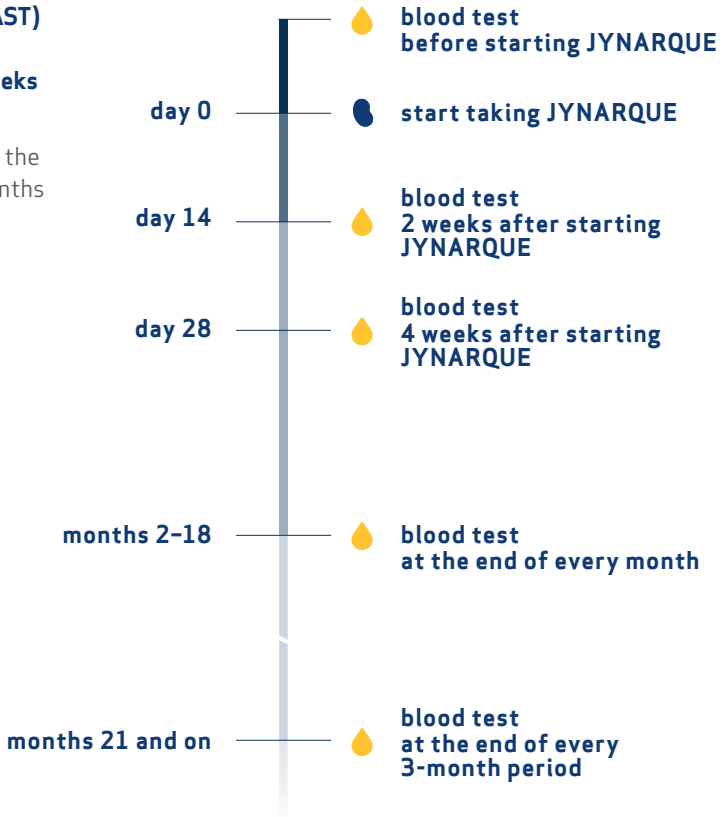
Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

To manage the risk of liver injury, JYNARQUE® (tolvaptan) is available through a restricted distribution program called the JYNARQUE REMS program

To become certified to prescribe JYNARQUE, you must enroll in the JYNARQUE Risk Evaluation and Mitigation Strategy (REMS) Program. Patients must also enroll in the JYNARQUE REMS Program. The purpose of REMS is to reduce the risk of hepatic injury for patients taking JYNARQUE.

Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation.

After that, monitor monthly for the first 18 months and every 3 months thereafter.



Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

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

Dosing and Administration

Patients should be advised to take JYNARQUE® (tolvaptan) 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 plus 30 mg, then to 90 mg plus 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
- **OATP1B1/3 and OAT3 Transporter Substrates:** Patients who take JYNARQUE should avoid concomitant use with OATP1B1/B3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide), as the plasma concentrations of these substrates may be increased.
- **BCRP Transporter Substrates:** Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE, should avoid concomitant use with BCRP substrates (e.g., rosuvastatin)
- **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 18-19.

Prescribing JYNARQUE® (tolvaptan)

For illustrative purposes only. Final packages may vary.

Initial dose prescription	Titration step prescription	Target dose prescription
60 mg DAILY	90 mg DAILY	120 mg DAILY

JYNARQUE is available to patients through limited distribution specialty pharmacies

allianceRx Walgreens + PRIME

Avella Specialty Pharmacy

PANTHERx RARE

The 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

Eligible patients pay no more than $10 per month with JYNARQUE copay support*

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.

*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.

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

As part of patient counseling, review the JYNARQUE® (tolvaptan) Medication Guide with every patient

- Advise patients that blood testing is required before starting JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly during the first 18 months of therapy, and every 3 months thereafter, as a requirement to reduce the risk of serious liver injury. Advise patients to immediately stop taking JYNARQUE and notify their doctor if they have symptoms or signs of hepatic injury
- Advise patients that JYNARQUE is only available through the JYNARQUE REMS Program. Patients must enroll in the program and comply with ongoing monitoring requirements. JYNARQUE is available only from REMS-certified specialty pharmacies. Provide patients with the telephone number and website for information on how to obtain the product
- Advise patients to drink water to avoid thirst, throughout the day and night. Patients should stop taking JYNARQUE and notify their healthcare provider if they have symptoms or signs of sodium imbalance or dehydration. Advise patients that if they cannot drink enough water for any reason, they should stop taking JYNARQUE and inform their healthcare provider right away
- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy. Advise women not to breastfeed during treatment with JYNARQUE
- Advise patients to inform you of their medical conditions and the medications they are taking
- Ensure that patients understand how to take JYNARQUE
- Advise patients to refrain from consuming grapefruit juice, which may affect how JYNARQUE is metabolized
- Counsel patients about the most common adverse reactions they may experience when taking JYNARQUE, including thirst, polyuria, pollakiuria, nocturia, and polydipsia

Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

Based on feedback from your peers, consider sharing the tips below

Starting and Continuing Treatment

- Prior to starting treatment, consider advising your patients to increase their normal water intake[30]
- Consider initiating JYNARQUE when patients are not at work, such as a weekend day[30]
- Take into account patients' individual lifestyles and daily activities when assessing the dosing schedule and titration of JYNARQUE. Advise patients that titration is based on tolerability

Diet and Exercise

- Communicate the general health benefits of regular exercise
- Consider advising your patients that moderate reductions in the ingestion of protein and sodium may help to reduce urine volume. Dietary counseling may help patients tolerate the aquaretic side effects of JYNARQUE[30-32]
- Consider advising patients to adjust their meal schedule and amount of protein and sodium intake to change the timing of the highest urine output[31,32]
- Talk with your patients about avoiding beverages with high sugar or fat content (eg, sodas, fruit juices, whole milk) while taking JYNARQUE to avoid excessive caloric intake[30]

Getting Ready for Shipment

- Let your patients know that JYNARQUE will be shipped to them each month, and advise them about which specialty pharmacy will send their prescription
- Inform patients that the specialty pharmacy will call them, and that they 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 liver enzyme testing by sending reminders and providing 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
- Suggest carrying a water bottle at work, in the car, and during physical activities to help them stay hydrated
- Mobile apps like SitOrSquat, Flush, or Toilet Finder can help patients locate nearby restrooms while away from home
- Sharing their experiences with family, friends, and healthcare team can help patients feel more comfortable with treatment; being open about the condition is crucial to managing the emotional impact

Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

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.

Continued on the next page

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
- **OATP1B1/3 and OAT3 Transporter Substrates:** Patients who take JYNARQUE should avoid concomitant use with OATP1B1/B3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide), as the plasma concentrations of these substrates may be increased.
- **BCRP Transporter Substrates:** Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE, should avoid concomitant use with BCRP substrates (e.g., rosuvastatin)
- **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**.

JYNARQUE® (tolvaptan) is indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD

- Studied in the 2 largest clinical trials of patients with ADPKD, which included patients across CKD stages 1-4[2,33,34]
- JYNARQUE is a selective vasopressin V_2-receptor antagonist
- JYNARQUE has been prescribed to more than 5500 patients, by over 2500 physicians[35]

Eligible commercially insured patients pay no more than $10 per 1-month supply for JYNARQUE*

Visit **JYNARQUEhcp.com** to learn more about ADPKD and identify appropriate patients for JYNARQUE.

SELECT 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**

Please see **IMPORTANT SAFETY INFORMATION** on pages 18-19.

*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.

If you have an appropriate patient for JYNARQUE who might benefit from speaking with a patient who is already taking JYNARQUE, and hearing their experience, please reach out to your Sales Representative

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Otsuka America Pharmaceutical, Inc.

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

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