

## ASN Comments on Proposed Rules Governing Payment and Quality Measurement in the ESRD Program

By David L. White

Every summer, the Centers for Medicare & Medicaid Services (CMS) releases the proposed End-Stage Renal Disease (ESRD) Prospective Payment System (PPS) and Quality Incentive Program (QIP) rule that will govern payment and quality measurement in the ESRD program in the calendar year (CY) ahead. This summer was no different, so ASN recommended adjustments to the proposal during the 60-day comment period required by law under the Administrative Procedure Act, which governs rulemaking at the federal level. Currently, more than 800,000 Americans experience kidney failure, including more than 550,000 receiving dialysis and more than 200,000 living with a kidney transplant.

As always, ASN takes advantage of the open comment process to refocus the administration on the vast impact of kidney diseases on 37 million Americans and their family members. It is also an important opportunity to underscore the fact that kidney diseases and kidney failure disproportionately impact historically marginalized populations and minorities, including those who are American Indian or Alaska Native, Asian, Black, Hispanic or Latinx, and Native Hawaiian and Other Pacific Islander; people with lower incomes; and older adults, underlying and exacerbating existing disparities. These and other factors explain why it is critical that the CMS ESRD program promotes equitable access to optimal kidney care.

The proposals discussed in ASN's letter (1) and this article are expected to be finalized around the same time as Kidney Week 2024.

### AKI site of care

After several years of advocacy by ASN, CMS proposed to extend the home dialysis benefit to individuals with acute kidney injury (AKI) for either peritoneal dialysis (PD) or home hemodialysis (HD). For patients with AKI requiring kidney replacement therapy, ASN advocated for allowing home dialysis as patients transition to home (from hospitals or postacute or in-center transitional dialysis facilities), and the corresponding Medicare payment should be allowed when the nephrologist and patient agree that a particular patient with AKI can safely dialyze at home.

ASN views home therapy as supervised care that is of at least similar quality and intensity to in-center HD and highlighted the commitment to ensuring the success of all patients with AKI requiring dialysis (AKI-D), regardless of whether they are receiving dialysis in the home or in an HD facility. In these circumstances, intensive training for home dialysis should also be reimbursed by Medicare, via the addition of Current Procedural Terminology training codes 90989 and 90933 being added to the telehealth list. (Because there is no relative value unit attached to these codes, clinicians who are dependent on the relative value unit system to quantify their clinical work have a difficult time receiving credit for the work that they perform in the supervision of home dialysis training.)

ASN expressed concerns regarding an Add-on Payment Adjustment for Training of patients with AKI being added to the same payment as the proposed payment amount in 2025 for in-center dialysis: \$273.20. However, CMS also proposed to extend an add-on payment adjustment for home and self-dialysis training at the same rate

as patients with ESRD, on a budget-neutral basis, which results in a proposed AKI CY 2025 base rate (for all dialysis modalities) of \$264.70 (\$273.20 - \$8.50, with \$8.50 being the estimated add-on training adjustment). The problem with the adjustment, ASN pointed out, was CMS' math. The agency assumed that the number of patients with AKI going to home dialysis would be the same rate as all patients with ESRD receiving home dialysis in the fourth quarter of 2022: 15.4%. ASN asserted to CMS that "It is highly unlikely that the AKI home dialysis rate will equal the over-

all ESRD home dialysis rate, especially not in the first years of this new policy." Nephrologists evaluating the proposed rule felt that it is highly unlikely that there will be a significant number of individuals with AKI initiating home PD. ASN expressed concern that such an out-of-portion payment adjustment could impact modality choices for these patients for whom PD is an important patient-centered option. Patients with AKI-D are reimbursed lower than incident patients with ESRD, reflecting noninclusion of the incident patient modifier. While this is required by law, it emphasizes

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### 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.

**Hypertatremia, Dehydration and Hypovolemia:** JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypertatremia. 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

that further deductions from the reimbursement for HD for AKI-D would be financially unviable.

ASN volunteered its AKINow Committee to work with CMS on accurate predictions of the uptake of home dialysis for AKI-D. Additionally, CMS correctly pointed out that “ESRD” and “AKI” are not interchangeable and that the Conditions for Coverage (CfCs) for dialysis facilities need to be aligned with the changes proposed in the rule. ASN believes that CfCs need updating (last updated in 2008) and urged CMS to engage the kidney care community in a broader dialogue on a range of potential updates to CfCs.

### Dialysis bundled payment shortcomings

ASN expressed strong concern over an inadequate Medicare bundled payment for dialysis. In its March “Report to the

Congress,” the Medicare Payment Advisory Commission (MedPAC) estimated a margin of zero for 2024 (2). MedPAC’s finding means that there are many facilities with a margin below zero. Given the significantly increasing costs, it poses challenges for many facilities to be able to adjust to unexpected events when they occur or, in some cases, to be able to continue providing services at their historic levels. A decrease in access to dialysis presents a grave concern for all patients regardless of payor. Other concerns identified by ASN in the proposed rule include the following:

- 1 **CMS proposed using the outlier policy as payment policy for innovation.** ASN expressed alarm that CMS’ proposal to address innovative payment in the proposed rule by expanding products eligible for outlier payments did not represent a sustainable ESRD PPS policy for ade-

quate funding for innovative drugs, biologics, and devices as covered by the Transitional Drug Add-on Payment Adjustment (TDAPA) under the ESRD PPS for certain new renal dialysis drugs and biological products. As MedPAC stated, the outlier policy is essentially stop-loss insurance, and it is not meant to establish accurate and adequate payment for new medically necessary services.

ASN recommended that CMS support the approach in the proposal outlined in section 201 of Senate bill 4469, the “Chronic Kidney Disease Improvement in Research and Treatment Act of 2024” (3). This proposal would require CMS in a nonbudget neutral manner to:

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## JYNARQUE® (tolvaptan) has been proven effective in the 2 largest clinical trials of over 2800 patients with ADPKD across CKD stages 1–4<sup>1-3</sup>

### TEMPO 3:4 Trial— A 36-month trial in patients with CKD Stages 1, 2, and 3<sup>2,4</sup>

**49% reduction**  
of total kidney volume 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.<sup>†</sup>

**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<sup>†</sup>); TKV  $\geq 750$  mL; creatinine clearance  $\geq 60$  mL/min. Patients were treated for up to 3 years. **The primary endpoint was annual rate of change in the total kidney volume.**<sup>4</sup>

### REPRISE Trial— A 12-month trial of patients with CKD late Stage 2 to early Stage 4<sup>3,5</sup>

**35% reduction**  
in decline of kidney function  
vs placebo

(treatment effect: 1.3 mL/min/1.73 m<sup>2</sup>/  
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<sup>2</sup> if younger than age 56; or eGFR between 25 and 44 mL/min/1.73 m<sup>2</sup>, plus eGFR decline  $> 2.0$  mL/min/1.73 m<sup>2</sup>/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.**<sup>3,6</sup>

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

\*Data only included those patients who remained in the study for 3 years; effect in those who discontinued is unknown.<sup>2</sup>

<sup>†</sup>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.

<sup>†</sup>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.<sup>7,8</sup>

(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<sub>2</sub>-Receptor Agonist:** Tolvaptan interferes with the V<sub>2</sub>-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V<sub>2</sub>-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 Brief Summary of FULL PRESCRIBING INFORMATION, including BOXED WARNING, on the following page.

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



**References:** 1. Data on file. TOLV-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. 2. Torres VE, Chapman AB, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *N Engl J Med.* 2012;367(25):2407-2418. 3. Torres VE, Chapman AB, Devuyst O, et al; for the REPRISE Trial Investigators. *N Engl J Med.* 2017;377(20):1930-1942. 4. Torres VE, Meijer E, Bae KT, et al. *Am J Kidney Dis.* 2011;57(5):692-699. 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. Belibi FA, Edelstein CL. *J Am Soc Nephrol.* 2009;20(1):6-8. 8. Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM. *Lancet.* 1994;343(8901):824-827.

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# Policy Update

## ASN Comments on Proposed CMS Rules

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- Establish a permanent post-TDAPA to the base rate for a new drug or biological product that comes within an existing functional category.
- Calculate the post-TDAPA using the most recent 12-month period of utilization data for the product and the most recent available full calendar quarter of average sales price (ASP).
- Update the adjustment amount annually to account for inflationary changes.
- Apply the adjustment amount immediately upon the expiration of the TDAPA period.

ASN maintains that the ESRD PPS as currently structured stifles innovation for a population that already experiences

extreme health disparities and issues of access. As a result of recent policies, patients with chronic kidney disease-associated pruritus are not able to access the only US Food and Drug Administration-approved treatment indicated specifically to treat this disease. The manufacturer of difelikefalin (Korsuva) has indicated it will cease all research and development in the area of chronic kidney disease, reflecting low use due to payment policy.

- Orals in the ESRD PPS bundle present challenges.** ASN has repeatedly voiced its concerns to CMS about including oral-only phosphate binders and other phosphate-lowering drugs in the ESRD PPS for many reasons and supports efforts in Congress to delay that occurrence, but CMS again requested comments on a payment approach. To maintain consistency with the treatment of calcimimetics during their first 2 years of TDAPA, to align with the way Medicare reimburses for drugs and biologics under the Hospital Outpatient PPS's pass-through policy, and to minimize

administrative burden on CMS and care facilities, ASN recommended that CMS adopt the methodology outlined in the Social Security Act section 1847A (4). This methodology sets payment at ASP + 6%; if ASP is not available, the payment is based on the wholesale acquisition cost.

ASN has made clear to CMS that it believes that adding phosphate binders and phosphate-lowering drugs to the bundle will have a negative impact on patients. ASN emphasized that phosphate binders and phosphate-lowering drugs must be taken outside of the facility, typically when a patient eats. Congress has recognized the challenges of including these drugs in the ESRD PPS when it has repeatedly restricted CMS from adding them. Furthermore, there will not be an actionable solution present for the distribution of phosphate-lowering agents to patients residing in nursing homes or other facilities.

- There is also the problem of no dispensing fees.** CMS recognized in the proposed rule's preamble that "dispensing fees and other costs are not currently included in the ESRD PPS base rate for phosphate binders" (5). As the Government Accountability Office found in its 2023 report, dialysis facilities will incur significant costs that are not included in the base rate if phosphate binders are added to the ESRD PPS bundled reimbursement (6). These costs include the following:

- paying pharmacy charges to obtain the drugs through them
- mailing fees either in terms of obtaining the drugs from pharmacies or sending the drugs directly to patients' homes, which is where they are taken
- incurring storage costs associated with maintaining the drugs at the dialysis facility if the decision is to distribute the drugs to patients during their dialysis treatment sessions
- complying with state pharmacy laws; for example, some states, like Alabama, do not allow dialysis facilities to distribute oral drugs, so there are additional contracting costs incurred
- supporting the provision of a significant volume of pills to patients so that they have the amount they need at every meal and snack
- adjusting drug supplies when a physician changes a patient's prescription to another product (which often occurs)
- absorbing costs of unused medications when patients are hospitalized, transfer to other facilities, die, or receive a kidney transplant

ASN detailed the differing policies within CMS programs and recommended that CMS adopt the straightforward and transparent ASP + 6% policy that it relies on in other parts of the Medicare program. As an alternative, CMS could consider using the same flat rate supply fee used for other oral Part B drugs that are supplied as part of a physician service.

### QIP

CMS added three new health equity-focused quality measures in the CY 2024 ESRD PPS final rule (88 FR 76437-76446 and 76466-76480) to ESRD QIP (5). CMS is now soliciting feedback on the creation of a Health Equity Adjustment. ASN applauded CMS for its efforts to improve health equity among the population with ESRD receiving facility-based dialysis, given long-standing disparities among this population. ASN posed questions to CMS about the efficacy and logistics of the proposal. It remains unclear if CMS will delay this effort to provide time to improve the proposal.

ASN supported CMS' proposal to disaggregate the Kt/V Dialysis Adequacy measure into four distinct components, each evaluated against its own performance standards. ASN's analysis found that the approach acknowledges the complexity of dialysis adequacy and allows for a more nuanced assessment. By distinguishing

JYNARQUE® (tolvaptan) tablets for oral use  
Brief summary of PRESCRIBING INFORMATION. See full prescribing information for JYNARQUE.

#### 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 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 restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program.

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

**CONTRAINDICATIONS:** JYNARQUE is contraindicated in patients:

- With a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease.
- Taking strong CYP 3A inhibitors.
- With uncorrected abnormal blood sodium concentrations.
- Unable to sense or respond to thirst.
- Hypovolemia.
- Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product.
- Uncorrected urinary outflow obstruction.
- Anuria.

#### WARNINGS AND PRECAUTIONS

**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 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 reintitiated 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.

**JYNARQUE REMS Program:** JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program, because of the risks of liver injury. Notable requirements of the JYNARQUE REMS Program include the following:

- Prescribers must be certified by enrolling in the REMS program.
- Prescribers must inform patients receiving JYNARQUE about the risk of hepatotoxicity associated with its use and how to recognize the signs and symptoms of hepatotoxicity and the appropriate actions to take if it occurs.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements.
- Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive JYNARQUE.

**Hypertatremia, Dehydration and Hypovolemia:** JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypertatremia. Therefore, ensure abnormalities in sodium concentrations are corrected prior to initiation of therapy.

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.

During JYNARQUE therapy, if serum sodium increases above normal range or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, then suspend JYNARQUE until serum sodium, hydration status and volume status is within the normal range.

**Co-Administration with Inhibitors of CYP 3A:** Concomitant use of JYNARQUE with drugs that are moderate or strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and cobicistat) increases tolvaptan exposure. Use with strong CYP 3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors.

#### ADVERSE REACTIONS

**Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. JYNARQUE has been studied in over 3000 patients with ADPKD. Long-term, placebo-controlled safety information of JYNARQUE in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo for at least 12 months across both studies.

**TEMPO 3-4 -NCT04289448: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD.** The TEMPO3-4 trial employed a two-arm, 2:1 randomization to tolvaptan or placebo, titrated to a maximally-tolerated total daily dose of 60-120 mg. A total of 961 subjects with rapidly progressing ADPKD were randomized to JYNARQUE. Of these, 742 (77%) subjects who were treated with JYNARQUE remained on treatment for at least 3 years. The average daily dose in these subjects was 96 g daily.

Adverse events that led to discontinuation were reported for 15.4% (148/961) of subjects in the JYNARQUE group and 5.0% (24/483) of subjects in the placebo group. Aquaretic effects were the most common reasons for discontinuation of JYNARQUE. These included polyuria, polyuria, or nocturia in 63 (6.6%) subjects treated with JYNARQUE compared to 1 subject (0.2%) treated with placebo.

Table 1 lists the adverse reactions that occurred in at least 3% of ADPKD subjects treated with JYNARQUE and at least 1.5% more than on placebo.

Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%)*	Annualized Rate†	Number of Subjects	Proportion (%)*	Annualized Rate†
Increased urination‡	668	69.5	28.6	135	28.0	10.3
Thirst†	612	63.7	26.2	113	23.4	8.7
Dry mouth	154	16.0	6.6	60	12.4	4.6
Fatigue	131	13.6	5.6	47	9.7	3.6
Diarrhea	128	13.3	5.5	53	11.0	4.1

Table 1: TEMPO 3-4, Treatment Emergent Adverse Reactions in ≥3% of JYNARQUE Treated Subjects with Risk Difference ≥ 1.5%, Randomized Period

Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%)*	Annualized Rate†	Number of Subjects	Proportion (%)*	Annualized Rate†
Dizziness	109	11.3	4.7	42	8.7	3.2
Dyspepsia	76	7.9	3.3	16	3.3	1.2
Decreased appetite	69	7.2	3.0	5	1.0	0.4
Abdominal distension	47	4.9	2.0	16	3.3	1.2
Dry skin	47	4.9	2.0	8	1.7	0.6
Rash	40	4.2	1.7	9	1.9	0.7
Hyperuricemia	37	3.9	1.6	9	1.9	0.7
Palpitations	34	3.5	1.5	6	1.2	0.5

\*100x (Number of subjects with an adverse event/N)

†100x (Number of subjects with an adverse event/Total subject years of drug exposure)

‡Thirst includes polydipsia and thirst

§Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria

**REPRISE-NCT02160145: A Phase 3, Randomized-Withdrawal, Placebo-Controlled, Double-Blind, Trial in Late Stage 2 to Early Stage 4 ADPKD.** 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 subjects 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. **Liver Injury:** 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.

**Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of tolvaptan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

**Hepatobiliary Disorders:** Liver failure requiring transplant

**Immune System Disorders:** Anaphylaxis

#### DRUG INTERACTIONS

**CYP 3A Inhibitors and Inducers:** CYP 3A Inhibitors: Tolvaptan's AUC was 5.4 times as large and Cmax was 3.5 times as large after co-administration of tolvaptan and 200 mg ketoconazole. Larger doses of the strong CYP 3A inhibitor would be expected to produce larger increases in tolvaptan exposure. Concomitant use of tolvaptan with strong CYP 3A inhibitors is contraindicated. Dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE. **Strong CYP 3A Inducers:** Co-administration of JYNARQUE with strong CYP 3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP 3A inducers.

**V<sub>2</sub>-Receptor Agonist:** As a V<sub>2</sub>-receptor antagonist, tolvaptan will interfere with the V<sub>2</sub>-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V<sub>2</sub>-agonist.

#### USE IN SPECIFIC POPULATIONS

**Pregnancy: Risk Summary:** Available data with JYNARQUE use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits at exposures approximately 4- and 1-times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 90/30 mg. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. In rats, reduced fetal weights and delayed fetal ossification occurred at 17-times the human exposure. In rabbits, increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations occurred at approximately 3-times the human exposure. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20% of clinically recognized pregnancies, respectively.

**Lactation: Risk Summary:** There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary. Because of the potential for serious adverse reactions, including liver toxicity, electrolyte abnormalities (e.g., hypertatremia), hypotension, and volume depletion in breastfed infants, advise women not to breastfeed during treatment with JYNARQUE.

**Pediatric Use:** Safety and effectiveness of JYNARQUE in pediatric patients have not been established.

**Geriatric Use:** Clinical studies of tolvaptan did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Use in Patients with Hepatic Impairment:** Because of the risk of serious liver injury, use is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease which was present in 60% and 66% of patients in TEMPO 3-4 and REPRISE, respectively. No specific exclusion for hepatic impairment was implemented in TEMPO 3-4. However, REPRISE excluded patients with ADPKD who had hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease.

**Use in Patients with Renal Impairment:** Efficacy studies included patients with normal and reduced renal function. TEMPO 3-4 required patients to have an estimated creatinine clearance ≥60 mL/min, while REPRISE included patients with eGFR<sub>CR<sub>CL</sub></sub> ≥25 to 65 mL/min/1.73m<sup>2</sup>.

**OVERDOSAGE:** Single oral doses up to 480 mg (4 times the maximum recommended daily dose) and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia. In patients with suspected JYNARQUE overdose, assessment of vital signs, electrolyte concentrations, ECG and fluid status is recommended. Continue replacement of water and electrolytes until aquaretic abates. Dialysis may not be effective in removing JYNARQUE because of its high binding affinity for human plasma protein (>98%).

#### PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

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

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among various aspects of Kt/V, this proposal facilitates a more accurate reflection of patient-specific needs and treatment efficacy. However, ASN has longstanding concerns about the application of Kt/V in assessing PD adequacy, particularly considering existing guidelines and patient outcomes.

ASN continued to express concern over the number of measures in QIP particularly the following:

- 1 **In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey Administration (clinical measure).** ASN continues to express concern over the low response rate to ICH CAHPS. To reduce the burden on patients, ASN requested the form be shortened and that CMS field the survey once a year and not twice. Finally, to empower patients, ASN encouraged CMS to allow facilities to see deidentified results of the surveys so that they can respond to the specific patient concerns with some level of patient permission. Patient members of several technical expert panels have recommended this step.
- 2 **Standard Readmission Ratio (SRR) (clinical measure).** ASN remains concerned that SRR might mislead patients, care partners, and health care practitioners due to its wide confidence interval. This variability can lead to inaccurate facility classifications and fail to accurately reflect actual performance. ASN noted that the current measure also poses challenges for small facilities, as their scores can be heavily influenced by random variability. ASN urged CMS to transition to the use of the underlying readmission rate, which can be properly risk adjusted in the same way that the standardized mortality rate has been and allow within-facility year-to-year comparisons.
- 3 **Standardized Transfusion Ratio (STrR) (clinical measure).** ASN expressed concerns that the STrR measure lacks validity and believes it should be suppressed. ASN, while appreciative that CMS has acknowledged this concern, remained troubled that CMS has not addressed the low reliability of the data on transfusions.
- 4 **Standardized Hospitalization Ratio (clinical measure).** ASN agreed that hospitalization rates are crucial indicators of quality for both patients and facilities but also strongly urged CMS to implement a genuinely risk-standardized hospitalization rate measure to prevent misclassifying facilities and misleading patients.
- 5 **Clinical Depression Screening and Follow-up (reporting measure).** ASN recognized that identifying and treating mental health conditions among patients receiving dialysis are critical to ensuring optimal health and clinical outcomes. ASN expressed major concerns about the ability of dialysis units to treat depression in isolation, without additional support and resources. As a first step, ASN

proposed that CMS consider clarifying opportunities for and supporting expanded access to mental health services that can occur either on-site in the dialysis facility (e.g., in a private room before or after treatments) or via telemedicine for patients on dialysis.

- 6 **National Healthcare Safety Network (NHSN) Dialysis Event (reporting measure).** ASN supports CMS' proposal to remove the NHSN Dialysis Event reporting measure from the ESRD QIP measure set beginning with payment year 2027.
- 7 **NHSN Bloodstream Infection (BSI) in Patients on HD (clinical measure).** Research from the Centers for Disease Control and Prevention, the measure's developer, as well as from CMS and other sources, indicates that the measure lacks both validity and reliability. Previously, ASN has recommended that CMS transition the NHSN BSI measure to a reporting measure while forming a technical expert panel to address its shortcomings.
- 8 **Screen Positive Rate for Social Drivers of Health (reporting measure).** ASN applauds CMS' commitment to addressing health care disparities and supporting these measure concepts. ASN strongly supports the implementation of screening measures for social drivers of health for patients on dialysis, recognizing their potential to improve patient care. However, ASN also encouraged CMS to evaluate the impact of public reporting of the percentage of patients in each dialysis facility who screen positive in various domains. ASN fears that this publicity may lead patients to either avoid answering or provide inaccurate responses, especially within the close-knit environment of a dialysis facility.

To keep track of ASN's policy efforts related to these proposals, follow coverage in *Kidney News* and the ASN podcast feed, and visit ASN's policy webpage (<http://www.asn-online.org/policy>). For real-time updates from ASN Policy, follow @ASNAdvocacy on X. ■

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#### Summary of ASN recommendations in its CY 2025 comment letter (1)

- Finalize site of care proposal for individuals with AKI.
- Revise proposed Add-on Payment Adjustment for Training.
- Support proposed conditions for coverage for dialysis facilities but need to go further.
- Address dialysis bundled payment shortcomings.
  - Payment policy for innovation does not equate to the outlier policy—do not finalize.
  - Dispensing fees for orals in the bundle are needed if oral-only agents are included in PPS.
  - The policy of the current base rate does not include dispensing fees for phosphate binders.
- Convene community to improve the proposed Health Equity adjustment.
- Support replacing the Kt/V Dialysis Adequacy comprehensive clinical measure (measuring how much urea is removed during dialysis) with four separate measures.
- Address additional ESRD QIP issues.

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