

FDA Approves Two New AV Fistula Devices

The U.S. Food and Drug Administration (FDA) has granted marketing approval for two catheter devices used in dialysis. Both the everlinQ endoAVF System, which uses two catheters, and the Ellipsys Vascular Access System with a single catheter are designed to create arteriovenous (AV) fistulas, using an energy source to forge the connection between blood vessels in a patient's arm. Traditionally a central venous catheter for dialysis patients is created through a surgical process. An AV graft uses a tube or cadaveric blood vessel to create a bridge between artery and vein.

The FDA reviewed data for the everlinQ endoAVF System from a non-randomized, multi-center study of 60 patients, and also considered supporting data from three other studies. The device has been used by clinicians outside the United States.

TVA Medical (Austin, TX) manufactures the everlinQ system, which works as a series of spaced magnets in each catheter, one venous and one arterial, that are designed to attract and align. The patient is then ready for a radiofrequency pulse deployed at the desired spot between the close brachial (arm) blood vessels.

In the main study of the everlinQ endoAVF System, 52 patients (86.7%) met the criteria for a usable AV fistula within three months after the procedure. Almost all patients (96.7%) required an additional procedure at the time the fistula was created, and 28.3% of patients required an additional procedure (such as balloon angioplasty) in the first 12 months to maintain the fistula, the FDA noted.

The Ellipsys Vascular Access System is a product of Avenu Medical, based in San Juan Capistrano, CA. The single catheter delivers a small amount of thermal energy

that fuses a permanent connection between the vein and artery.

The FDA reviewed data from a non-randomized, U.S. multicenter study of 103 patients, of whom 92 patients (89.3%) met the criteria for a usable AV fistula within three months. Almost all patients (96.1%) required an additional procedure (such as balloon angioplasty) in the first 12 months, the FDA reported.

Both systems were reviewed through the De Novo premarket review pathway for low-to-moderate risk devices of a new type. ■

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.

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.

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.

Further information, including a list of qualified pharmacies/distributors, is available at: www.JYNARQUEREMS.com or by telephone at 1-877-726-7220.

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypernatremia. 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.

In the two double-blind, placebo-controlled trials of patients with ADPKD, hypernatremia (defined as any serum sodium concentration >150 mEq/L) was observed in 4.0% versus 0.6% and 1.4% versus 0% of tolvaptan-treated versus placebo-treated patients, respectively. The rate of dehydration and hypovolemia in the two studies was 2.1% versus 0.7% and 2.3% versus 0.4% for tolvaptan-treated versus placebo-treated patients, respectively.

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 conivaptan) 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

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Serious Liver Injury
- Hypernatremia, Dehydration and Hypovolemia
- Drug Interactions with Inhibitors of CYP 3A

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.

JYNARQUE™ (tolvaptan)

TEMPO 3:4 -NCT00428948: 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 mg 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.

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 ¹	Number of Subjects	Proportion (%)	Annualized Rate ¹
Increased urination ²	668	69.5	28.6	135	28.0	10.3
Thirst ³	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
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

¹100x (Number of subjects with an adverse event/N)

²100x (Number of subjects with an adverse event/Total subject years of drug exposure)

³Thirst includes polydipsia and thirst

⁴Increased urination includes micturition urgency, nocturia, polyuria, 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 C_{max} 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.

OATP1B1/3 and OAT3 Transporter Substrates: The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/3 and OAT3 in vitro. Patients who take JYNARQUE should avoid concomitant use with OATP1B1/3 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).

V₂-Receptor Agonist: As a V₂-receptor antagonist, tolvaptan will interfere with the V₂-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V₂-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., hypernatremia), 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