Jynarque (tolvaptan)
Policy Number: C15434-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
12/19/2018	5/20/2020	5/20/2021
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J8499, C9339	RxPA	Q3 2020 20200722C15434-A

PRODUCTS AFFECTED:
Jynarque (tolvaptan)

DRUG CLASS:
Selective Vasopressin V2-Receptor Antagonists

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy
The recommendation is that medications in this policy will be for pharmacy benefit coverage and patient self-administered

AVAILABLE DOSAGE FORMS:
Jynarque TBPK 45 & 15MG, Jynarque TBPK 60 & 30MG, Jynarque TBPK 90 & 30MG (7 day and 28 day blister packs)

FDA-APPROVED USES:
Autosomal Dominant Polycystic Kidney Disease (ADPKD), Slow the progression of kidney function decline in adults at risk of rapidly progressing ADPKD

COMPENDIAL APPROVED OFF-LABELED USES:
None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
Autosomal Dominant Polycystic Kidney Disease (ADPKD)

REQUIRED MEDICAL INFORMATION:
A. AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE:

1. Documented diagnosis of autosomal dominant polycystic kidney disease (ADPKD) as confirmed by imaging (ultrasound, CT, or MRI) OR genetic testing
   AND
2. Prescriber attests that Member has rapidly progressing ADPKD as defined by reduced or declining renal function, high or increasing total kidney volume (height adjusted), confirmed by either: GFR decline of at least 5 mL/min/1.73 m^2 per year over 1 year and/or 2.5 mL/min/1.73 m^2 per year over a period of 5 years OR a total kidney volume increase of at least 5% per year confirmed by at least 3 repeated ultrasound or MRI measurements taken

at least 6 months apart
AND

3. Prescriber attests that pre-treatment laboratory results have been reviewed and are appropriate: Liver function laboratory values (ALT, AST and bilirubin) within the normal range (as required by the Jynarque REMS Program), Serum sodium concentration <150 mEq/L, Comprehensive metabolic panel and Blood pressure
   AND
4. Prescriber attests that Member does not have Stage 5 chronic kidney disease (CKD) [glomerular filtration rate (GFR) < 15 mL/min/1.73 m^2 or receiving dialysis
   AND
5. Prescriber attests that standard management of blood pressure has been addressed AND the member has been counseled regarding dietary sodium restriction, and increased fluid intake
   AND
6. Prescriber attest that member does not have any of the following contraindications: liver impairment or injury, member is concurrently taking a strong inhibitors of the CYP3A4, member does not have the ability to sense or respond to thirst, abnormal serum sodium (particularly hypernatremia), hypovolemia, concomitant use of diuretics, or uncorrected urinary outflow obstruction.

DURATION OF APPROVAL:
Initial authorization: 3 months, Continuation of authorization: 12 months

QUANTITY:
15mg/15mg blister card; 4 of [14 tablets (7day blister card)] OR 56 tablets (4 blister cards) / 28 days
30mg/15mg blister card; 4 of [14 tablets (7day blister card)] OR 56 tablets (4 blister cards) / 28 days
45mg/15mg blister card; 4 of [14 tablets (7day blister card)] OR 56 tablets (4 blister cards) / 28 days
60 mg / 30 mg blister card: 4 of [14 tablets (7day blister card)] OR 56 tablets (4 blister cards) / 28 days
90 mg / 30 mg blister card: 4 of [14 tablets (7day blister card)] OR 56 tablets (4 blister cards) / 28 days

15mg- max #30/30 days- if higher dose is needed, use blister pack
30mg max # 30/30 days- if higher dose is needed, use blister pack

Maximum of 120 mg/day

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a nephrologist or physicians specializing in the management of Autosomal Dominant Polycystic Kidney Disease (ADPKD) and is certified to prescribe Jaynarque by the REMS program

AGE RESTRICTIONS:
18 years of age and older

CONTINUATION OF THERAPY:
A. AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE:

1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)

AND

2. Prescriber attests to evidence of continuing improvement or positive clinical response to Jynarque therapy, such as kidney function decline has slowed (total kidney volume (TKV), albuminuria, onset or progression of hypertension, eGFR, etc.) and/or improvement in kidney pain.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Jynarque (tolvaptan) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Other labeled contraindications included:History, signs, or symptoms of significant liver impairment or injury (does not include uncomplicated polycystic liver disease), Uncorrected abnormal blood sodium concentrations, Concomitant use of strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, conivaptan), Hypovolemia, Anuria, Uncorrected urinary outflow obstruction and Baseline ALT, AST, and bilirubin laboratory abnormalities. See full prescribing information for complete boxed warning. JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported. Measure transaminases and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter. JYNARQUE is available only through a restricted distribution program called the JYNARQUE REMS Program.

OTHER SPECIAL CONSIDERATIONS:
None

BACKGROUND:
Autosomal Dominant Polycystic Kidney Disease (ADPKD) A multisystemic and progressive disorder characterized by cyst formation and enlargement in the kidney and extra-renal cysts in the liver, pancreas, spleen, seminal vesicles, ovary, and arachnoid. The main feature of ADPKD is a bilateral progressive increase in the number of cysts, which may lead to end-stage renal disease (ESRD). ADPKD is the fourth leading cause of ESRD. A genetically heterogeneous condition that involves at least 2 genes: mutations in PKD1 (chromosome region 16p13.3) and PKD2 (chromosome region 4q21). The most common hereditary kidney disorder, affecting approximately 12.5 million people worldwide in all ethnic groups. It is present at birth in 1 in 400 to 1 in 1,000 babies, and it affects approximately 400,000 people in the United States is responsible for up to 10% of patients in ESRD and a major burden for public health.
Jynarque (tolvaptan) is the first FDA-approved drug treatment that can slow kidney function decline in adult patients with a high risk of rapidly progressing ADPKD. Tolvaptan (also available as Samsca tablets) was previously approved for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium less than 125 mEq/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH). Refer to Samsca (tolvaptan) MCP-252.Tolvaptan is a selective vasopressin V2 receptor antagonist. The V2 receptor is located in the collecting ducts and the thick ascending limbs of the loops of Henle of the kidney. Binding of vasopressin to the V2 receptor in the kidney increases water permeability and sodium reabsorption; tolvaptan decreases these effects. If left untreated, ADPKD will lead to unregulated expansion of the renal tubule epithelium, resulting in the formation of fluid-filled cysts that grow and obstruct renal tubules, blood vessels, and lymphatics, which ultimately leads to kidney failure. Tolvaptan can slow disease progression by inhibiting cell proliferation in patients with ADPKD.The most common

adverse events in patients treated with Jynarque (incidence > 10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria, and polydipsia. Jynarque (tolvaptan) has a black box warning for serious and potentially fatal liver injury and is available only through a restricted distribution program called the Jynarque REMS Program. FDA approval was granted from two Phase III pivotal trials: the 3-year TEMPO 3:4 study (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) and the 1-year REPRISE study (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD) TEMPO 3:4 study Tolvaptan reduced the rate of decline in eGFR by 1.0 mL /min /1.73m2 /year as compared to placebo in patients with earlier stages of ADPKD. In the extension trial, eGFR differences produced by the third year of the TEMPO 3:4 trial were maintained over the next 2 years of Jynarque treatment. The primary endpoint in TEMPO 3:4 study was the intergroup difference for rate of change of total kidney volume (TKV) normalized as a percentage. The trial met its pre- specified primary endpoint of 3-year change in TKV ($p<0.0001$). REPRISE study Treatment with tolvatapan resulted in a change in estimated glomerular filtration rate (eGFR) of -2.3 mL/min/1.73m2/year from pre-treatment baseline to post-treatment follow-up, compared with -3.6 mL/min/1.73 m2/year among those who received placebo.The primary endpoint was the treatment difference in the change of eGFR from pretreatment baseline to post-treatment follow-up, annualized by dividing by each subject's treatment duration. In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow- up was −2.3 mL/min/1.73 m2/year with tolvaptan as compared with −3.6 mL/min/1.73 m2/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m2/year ($p <0.0001$).

The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Working Groups Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice (2016) Tolvaptan is recommended for adult ADPKD patients younger than 50 years with chronic kidney disease (CKD) stages 1 to 3a (estimated glomerular filtration rate [eGFR] greater than 45 mL/min/1.73 m²) who have demonstrated or who are likely to have rapidly progressing disease. Tolvaptan is not recommended for patients 30 to 40 years of age with CKD stage 1 (eGFR greater than 90 mL/min/1.73 m²) or patients 40 to 50 years of age with CKD stages 1 or 2 (eGFR greater than 60 mL/min/1.73 m²).

Summary of Clinical Evidence

Tolvaptan is indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD. Changes in surrogate markers (e.g., eGFR) demonstrate that tolvaptan slows progression of renal disease in patients with ADPKD. However, tolvaptan is not tolerated by all patients. The efficacy of tolvaptan in patients with ADPKD without preexisting hypertension is unknown. The most common adverse events in patients treated with Jynarque (incidence > 10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria, and polydipsia.

APPENDIX:

None

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

REFERENCES:

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4. Srivastava A, Patel N. Autosomal dominant polycystic kidney disease. American Academy of Family Physician. 2014;90(5):303-307
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7. Soroka S, Alam A, Bevilacqua M, et al. Assessing risk of disease progression and pharmacological management of autosomal dominant polycystic kidney disease – a Canadian expert consensus. Canadian Journal of Kidney Health and Disease. 2017;4:2054358117695784. doi:10.1177/2054358117695784.