Effective Date: 04/2021
Last P&T Approval/Version: 04/27/2022
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Policy Number: C21091-A

Tolvaptan

PRODUCTS AFFECTED

Jynarque (tolvaptan), Samsca (tolvaptan), tolvaptan

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines

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

DIAGNOSIS:
Autosomal Dominant Polycystic Kidney Disease (ADPKD), Hypervolemic and euvolemic hyponatremia

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review

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), confirmedby 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 takenat 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 normalrange (as required by the Jynarque REMS Program), Serum sodium concentration <150 mEq/L, Comprehensive metabolic panel and Blood pressureAND
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, abnormalserum sodium(particularly hypernatremia), hypovolemia, concomitant use of diuretics, or uncorrected urinary outflow obstruction.

B. HYPERVOLEMIC AND EUVOLEMIC HYPONATREMIA

1. Clinically significant hypervolemic or euvolemic hyponatremia as evidenced by:
   (a) Serum sodium less than 125 mEq/L [current or baseline value prior to beginning of therapy in hospital]
   OR
   (b) Serum sodium level ≥ 125 but patient is symptomatic and has resisted correction with fluid restriction
   AND
2. No concurrent use of strong CYP3A inhibitors [e.g., clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, telithromycin)]
   AND
3. Confirmation that member does not have underlying liver disease (including cirrhosis) or aCrCl less than 10ml/minute
   AND
4. Therapy will be (or was) initiate(d) or re-initiate(d) in a hospital within the past 30 days. If therapy has been initiated/re-initiated, member has not already received 30 days of tolvaptan therapy following the most recent hospitalization
   AND
5. Prescriber attests that member does not have any of the following contraindications: liver impairment or injury, member is concurrently taking a strong inhibitor of 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.

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.
AND

3. Jynarque ONLY: Prescriber attests that Liver function laboratory values (ALT, AST and bilirubin) will be monitored monthly for 18 months during treatment and every 3 months from then on.

B. HYPERVOLEMIC AND EUVOLEMIC HYPONATREMIA:
No renewal or continuation beyond 30 days. The duration of tolvaptan therapy should be limited to 30 days in order to minimize the risk of hepatic injury.
Additional authorization for treatment beyond 30 days is an EXCEPTION: [MOLINA MEDICAL DIRECTORREVIEW REQUIRED]

1. Continuing/ongoing treatment to prevent clinically significant hypervolemic or euvolemic hyponatremia due to conditions such as heart failure or SIADH
AND
2. Samsca (tolvaptan) was initiated or re-initiated in a hospital (for close monitoring of serum sodium)
AND
3. Chart notes and medical records supporting the rationale for therapy beyond 30 days, including documentation of improvement in member's condition as a result of therapy
AND
4. Prescriber acknowledges that Samsca should not be used for more than 30 days in order to minimize the risk of hepatic injury; however, Prescriber is determined to proceed with continuation of therapy. NOTE: At the discretion of the Molina Medical Director, a peer-to-peer consultation may be necessary

DURATION OF APPROVAL:
ADPKD-Initial authorization: 3 months, Continuation of authorization: 12 months
Hyponatremia- Initial authorization: 30 days. Continuation of Therapy: N/A. Therapy duration is limited to 30 days to limit hepatic injury risk associated with medication use.

PRESCRIBER REQUIREMENTS:
ADPKD- 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 tolvaptan by the REMS program
OR
Hyponatremia- Prescribed by or in consultation with a cardiologist, nephrologist, or endocrinologist

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
Jynarque (tolvaptan)
Blister cards (morning/afternoon dose)
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/30mg 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) / 28days

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

Samsca (tolvaptan)
60mg daily; 2 tablets per day

Maximum Quantity Limits –
Jynarque (tolvaptan)- Maximum 120 mg/day
Samsca (tolvaptan)- Maximum 60 mg/day

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Selective Vasopressin V2-Receptor Antagonists

FDA-APPROVED USES:
Jynarque (tolvaptan) indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)

Samsca (tolvaptan) indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia [serum sodium <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)

Important Limitations: Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA. It has not been established that SAMSCA provides a symptomatic benefit to patients

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

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 tolvaptan 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 mostcommon adverse events in patients treated with Jynarque (incidence > 10% and at least twice that

for placebo) were thirst, polyuria, nocturia, pollakiuria, and polydipsia.

Samsca (tolvaptan) is an oral non-peptide V2 vasopressin receptor antagonist indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (i.e., serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including in members with heart failure, cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH). Tolvaptan is initiated and re-initiated in a hospital and then continuedon an out-member basis and has been shown to induce short-term clinical improvements but has not demonstrated improvement in long-term outcomes such as mortality or hospitalizations.
Agents known to cause hyponatremia (not an all-inclusive list): amiodarone, antipsychotics, amitriptyline, bromocriptine, carbamazepine, ciprofloxacin, cisplatin, chlorpropamide, clofibrate, cyclophosmamide, desmopressin, haloperidol, ifosfamide, imatinib (high doses) interferon-alpha, interferon-gamm lorcainide, melphalan, methotrexate, monoamine oxidase inhibitors, nicotine, narcotics, NSAIDs, opiate, selective serotonin reuptake inhibitors (SSRIs), sodium valproate, thioridazine, thiothixene, tricyclic antidepressants, vasopressin, vinblastine, vincristine, vinorelbine

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of tolvaptan are considered experimental/investigational and
therefore, will follow Molina's Off- Label policy. Contraindications to Jynarque (tolvaptan) include: History of signs or symptoms of significant liver impairment or injury, does not include uncomplicated polycystic liver disease; concomitant use of strong CYP 3A inhibitors is contraindicated; uncorrected abnormal blood sodium concentrations; Inability to sense or respond to thirst; hypovolemia; hypersensitivity to tolvaptan or any of its components; uncorrected urinary outflow obstruction; and, anuria. Contraindications to Samsca (topvaptan) include: Use in patients with autosomal dominant polycystic kidney disease (ADPKD) outside of FDA-approved REMS; use in patients who are unable to respond appropriately to thirst; hypovolemic hyponatremia; concomitant use of strong CYP3A inhibitors; anuria; and, hypersensitivity.

OTHER SPECIAL CONSIDERATIONS:
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.

All other uses of Samsca (tolvaptan) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Hypersensitivity (e.g., anaphylactic shock, generalized rash) to tolvaptan or any component of the formulation. History, signs, or symptoms of significant liver impairment or injury (avoid use in members with underlying liver disease); Uncorrected abnormal blood sodium concentrations. Inability to sense or respond to thirst; Hypovolemic hyponatremia. Urgent need to raise serum sodium acutely; uncorrected urinary outflow obstruction; Anuria; Concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin); Creatinine clearance less than 10 mL/min (not recommended because drug effects on serum sodium levels are likely lost at very low levels of renal function).
Because of the risk of hepatotoxicity, tolvaptan (Samsca) should not be used for autosomal dominant polycystic kidney disease (ADPKD) outside of the FDA-approved REMS

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Jynarque TBPK 45 & 15MG, Jynarque TBPK 60 & 30MG, Jynarque TBPK 90 & 30MG (7 day and28-day blister packs), Samsca TABS 15MG, Samsca TABS 30MG

REFERENCES

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10. Gheorghiade M, Gottlieb SS, Udelson JE, et al; Tolvaptan Investigators. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. Am J Cardiol 2006;97(7):1064-7.
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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Continuation of Therapy Quantity Contraindication/Exclusions/Discontinuation	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file