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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. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (JYNARQUE ONLY):
   1. Documented diagnosis of autosomal dominant polycystic kidney disease (ADPKD)
      AND
   2. Prescriber attests or clinical reviewer has found that the member has rapidly progressing

ADPKD

NOTE: Rapidly progressing ADPKD as defined by reduced or declining renal function, or 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, 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 to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Jynarque (tolvaptan) include: history of signs or symptoms of significant liver impairment or injury, concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, telithromycin), unable to sense or respond to thirst, uncorrected abnormal blood sodium concentrations (particularly hypernatremia), hypovolemia, concomitant use of diuretics, uncorrected urinary outflow obstruction, anuria, hypersensitivity to tolvaptan or any of its components.]

B. HYPERVOLEMIC AND EUVOLEMIC HYPONATREMIA (SAMSCA, TOLVAPTAN ONLY):
1. Documentation of 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 member is symptomatic and has resisted correction with fluid restriction

AND
2. Prescriber attests or clinical reviewer has found that the member does not have underlying liver disease (including cirrhosis) or a CrCl less than 10 ml/minute
AND
3. Documentation therapy will be (or was) initiate(d) or re-initiate(d) in a hospital within the past 30 days AND member has not already received 30 days of tolvaptan therapy following the most recent hospitalization
AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Samsca (tolvaptan) include: concomitant use of strong of CYP3A inhibitors (e.g., clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, telithromycin), unable to respond appropriately to thirst, hypovolemic hyponatremia, anuria, hypersensitivity.]
AND
5. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

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.
   AND
4. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

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 DIRECTOR OR CLINICAL PHARMACIST REVIEW REQUIRED]
1. Documentation member requires continuing/ongoing treatment to prevent clinically significant hypervolemic or euvolemic hyponatremia due to conditions such as heart failure or SIADH
   AND
2. Documentation Samsca (tolvaptan) was initiated or re-initiated in a hospital (for close monitoring of serum sodium)
   AND
3. Documentation supporting the rationale for therapy beyond 30 days, including documentation of improvement in member's condition as a result of therapy [DOCUMENTATION REQUIRED]
   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 or Clinical Pharmacist, a peer-to- peer consultation may be necessary.
   AND
5. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

ADPKD: Initial authorization: 6 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. Continuation by exception only.

PRESCRIBER REQUIREMENTS:

ADPKD: Prescribed by, or in consultation with, a nephrologist or physician specializing in the management of Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Hyponatremia: Prescribed by or in consultation with a cardiologist, nephrologist, endocrinologist, or acute care physician (i.e., started in hospital)
[If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:
Jynarque (tolvaptan):
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
Blister pack (morning/afternoon dose): Max 56 tablets/28 days

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

Samsca (tolvaptan) is 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 and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
Limitations of use: 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 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.

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 continued on 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

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.

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, concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, telithromycin), unable to sense or respond to thirst, uncorrected abnormal blood sodium concentrations (particularly hypernatremia), hypovolemia, concomitant use of diuretics, uncorrected urinary outflow obstruction, anuria, hypersensitivity to tolvaptan or any of its components. Contraindications to Samsca (tolvaptan) include: Use in patients with autosomal dominant polycystic kidney disease (ADPKD) outside of FDA-approved REMS; concomitant use of strong of CYP3A inhibitors (e.g., clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, telithromycin), unable to respond appropriately to thirst, hypovolemic hyponatremia, anuria, hypersensitivity.

OTHER SPECIAL CONSIDERATIONS:
Jynarque (tolvaptan) has a BLACK BOX WARNING for 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 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.

Samsca (tolvaptan) has a BLACK BOX WARNING for A) initiate and re-initiate in a hospital and monitor serum sodium and B) not for use for autosomal dominant polycystic kidney disease (ADPKD). A) SAMSCA should be

initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. B) 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 TABS 15MG
Jynarque TABS 30MG
Jynarque TBPK 15MG
Jynarque TBPK 30 & 15MG
Jynarque TBPK 45 & 15MG
Jynarque TBPK 60 & 30MG
Jynarque TBPK 90 & 30MG
Samsca TABS 15MG
Samsca TABS 30MG
Tolvaptan TABS 15MG
Tolvaptan TABS 30MG

REFERENCES

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2. Samsca (tolvaptan) [prescribing information]. Rockville, MD: Otsuka America Pharmaceutical Inc; April 2021.
3. Torres VE, Chapman AB, Devuyst O, et al, for the TEMPO 3:4 trial investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367(25):2407- 2418.
4. Chapman AB, Devuyst O, Eckardt KU, et al. Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. 2/2017.
5. Srivastava A, Patel N. Autosomal dominant polycystic kidney disease. American Academy of Family Physician. 2014;90(5):303-307
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8. 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.
9. FDA Drug Safety Communications: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death. Safety announcement April30, 2013 UCM350084.

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11. Konstam MA, Gheorghiade M, Burnett JC Jr, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in members hospitalized for worsening heart failure: the EVEREST outcome trial.JAMA. 2007;297(12):1319-1331.
12. Schrier RW, Gross P, Gheorghiade M, et al; SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med2006;355(20):2099 112.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information	Q3 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Prescriber Requirements Quantity Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms	Q3 2023
REVISION- Notable revisions: Continuation of Therapy Quantity Contraindication/Exclusions/Discontinuation	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file